Supporting Information

Application of Palladium-Catalyzed Aryl C-H Alkylation in Total Synthesis of (-)-Berkelic Acid

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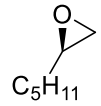
Table of Contents

1. General Information

All reactions were performed in oven-dried glassware fitted with rubber septa under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Methylene chloride (CH_2Cl_2) was distilled immediately before use from calcium hydride. Diethyl ether and tetrahydrofuran (THF) were distilled immediately before use from sodium-benzophenone ketyl. All other solvents were processed through the reference *Purification of Laboratory Chemicals (Seventh Edition)*. External bath temperatures were used to record all reaction temperatures. Silica gel (300~400 mesh) and petroleum ether, EtOAc, CH_2Cl_2 and MeOH were used for product purification by flash column chromatography. NMR spectra were recorded on Bruker 400 MHz (400 MHz for ^{1}H NMR and 101 MHz for ^{13}C NMR) spectrometers. Proton chemical shifts were reported relative to a residual solvent peak ($CDCl_3$ at 7.26 ppm) and carbon chemical shifts were reported relative to a residual solvent peak ($CDCl_3$ at 76.95 ppm) in order to compare with natural products conveniently. The following abbreviations were used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br = broad. High-resolution mass spectra (HRMS) were measured on a BruckerDaltonics Apex II 47e Specification (for HRMS). Chiral HPLC analysis was performed using an Agilent 1100 Alliance instrument. Fourier transform infrared spectra (FT-IR) were recorded on an Agilent Technologies Cary 630 FT-IR instrument. Optical rotations were measured on an Autopol IV, and are reported as $[\alpha]_D^T$ (concentration in g/mL solvent).

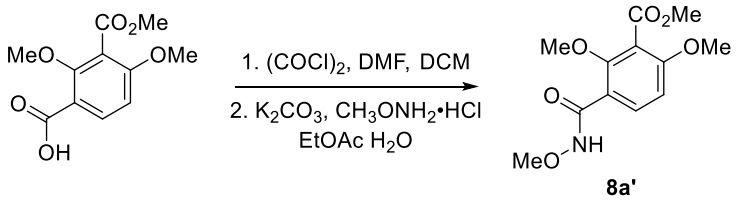
2. Experimental Procedures and Characterization Data of Compounds

(*R*)-(+)-2-Pentyloxirane (7): (*R*)-**7** and racemic **7** were prepared following a slightly modified procedure described in literature,[1] $[\alpha]_D^{20}$ = + 9.76 (c = 1.0 in $CHCl_3$), **^{1}H NMR (400 MHz, $CDCl_3$)** δ 2.93-2.85 (m, 1H), 2.74 (dd, *J* = 5.1, 4.0 Hz, 1H), 2.46 (dd, *J* = 5.0, 2.7 Hz, 1H), 1.56 – 1.38 (m, 4H), 1.36 – 1.27 (m, 4H), 0.95 – 0.84 (m, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ52.4, 47.1, 32.4, 31.6, 25.6, 22.5, 13.9. **IR (KBr, ν / cm^{-1})** 2935, 2922, 2864, 1444, 1273, 937, 834. **HRMS (ESI, m/z):** calcd for $C_7H_{15}O^+$ $[M+H]^+$: 115.1117; found: 115.1123.



(*R*)-7

Methyl 2,6-dimethoxy-3-(methoxycarbamoyl)benzoate (8a'):



8a'

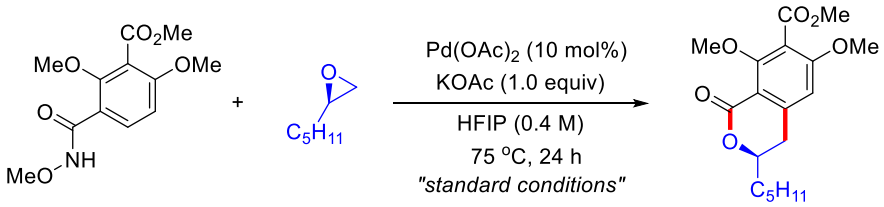
To a solution of the 2,4-dimethoxy-3-(methoxycarbonyl)benzoic acid (720 mg, 3.0 mmol) in dry DCM (10 mL) was added oxalyl chloride (0.30 mL, 3.6 mmol), dropwise at 0 °C, followed by a catalytic amount of dry DMF (2 drops). The reaction was stirred at room temperature until the acid was completely consumed. The solvent was removed under vacuum to afford the corresponding crude acyl chloride. Methoxyamine hydrochloride (334.1 mg, 4.0 mmol) was added to a biphasic mixture of K_2CO_3 (828 mg, 6.0 mmol) in a mixture of EtOAc (12 mL) and H_2O (6 mL). The mixture was cooled to 0 °C, and then acyl chloride in a minimum amount of EtOAc was added dropwise. The reaction was stirred at room temperature for 4 h. The organic phase was separated, and the aqueous phase was extracted for three times with EtOAc and dried over with Na_2SO_4. The solvent was evaporated and the mixture was directly purified by flash column chromatography with EtOAc to give **8a'** (685 mg, 85%) as a colorless oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.91 (s, 1H), 8.10 (d, *J* = 8.9 Hz, 1H), 6.81 (d, *J* = 8.9 Hz, 1H), 3.93 (s, 3H), 3.86 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.8, 162.9, 159.9, 155.7, 134.2, 117.9, 117.0, 107.5, 64.4, 63.4, 56.2, 52.8. **IR (KBr, ν / cm^{-1})** 2946, 1735, 1664, 1600, 1459, 1280, 1131, 928, 833. **HRMS (ESI, m/z):** calcd for $C_{12}H_{16}NO_6^+$ $[M + H]^+$: 270.0972; found: 270.0969.

The substrate scope of N-methoxybenzamide

alkylation of benzoic acid using Yu's method.[2]

A suspension of corresponding benzoic acid (0.1 mmol, 1.0 equiv), epoxide **7** (0.2 mmol, 2.0 equiv), KOAc (0.1 mmol, 1.0 equiv), Ac-*t*-leu-OH (20 mol%), $Pd(OAc)_2$ (10 mol%) and hexafluoroisopropanol (0.4 M) in a sealed tube was stirred at 75 °C. After 24 hours, the reaction mixture was concentrated and purified by column chromatography to give the product.

The detailed investigation of MPAA



8a' **(*R*)-7** (2.0 equiv) **(*R*)-9a**

Entry	the range of MPAA ligands (10 mol%)	yield[b] %
1	Ac-Leu-OH	17
2	Ac-*t*-Leu-OH	15
3	Ac-Ala-OH	28
4	Ac-Val-OH	24
5	Ac-Ile-OH	15
6	Ac-Gly-OH	30
7	Boc-Leu-OH	21
8	Boc-Ala-OH	25

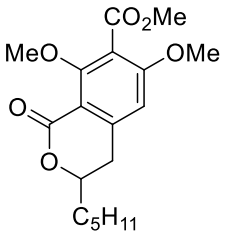
[a] MPAA = mono-N-protected amino acid ligands. [b] Isolated yields.

Procedure for alkylation of N-methoxybenzamide

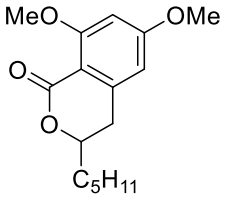
N-methoxybenzamide(0.1 mmol) and epoxide **7** (22 mg, 0.2 mmol), KOAc (9.8 mg, 0.1 mmol), $Pd(OAc)_2$ (2.2 mg, 10 mmol%), $CuCl_2$ (2.6 mg, 20 mmol%) and hexafluoro isopropanol (2.5 mL) in a sealed tube was stirred at 95 °C. After 24 hours, the reaction mixture was concentrated and purified by column chromatography to give the product.

Methyl 6,8-dimethoxy-1-oxo-3-pentylisochromane-7-carboxylate (9a):

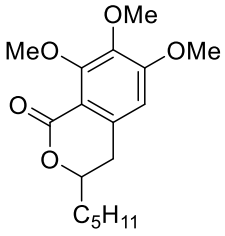
White solid (28.8 mg, 86% yield) **^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.51 (s, 1H), 4.43 – 4.33 (m, 1H), 3.91 (s, 3H), 3.91 (s, 3H), 3.87 (s, 3H), 2.97 – 2.80 (m, 2H), 1.89 – 1.77 (m, 1H), 1.72 – 1.61 (m, 1H), 1.60 – 1.49 (m, 1H), 1.49 – 1.37 (m, 1H), 1.36 – 1.27 (m, 4H), 0.89 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** 165.7, 161.7, 160.7, 160.2, 144.9, 118.8, 111.0, 105.2, 77.3, 63.2, 56.1, 52.6, 34.8, 34.5, 31.5, 24.5, 22.4, 13.9. **IR (KBr, ν / cm^{-1})** 2944, 1720, 1664, 1414, 1332, 1233, 1112, 931, 751. **HRMS (ESI, m/z):** calcd for $C_{18}H_{25}O_6^+$ [M + H]$^+$: 337.1646; found: 337.1643.



6,8-dimethoxy-3-pentylisochroman-1-one (9b): White solid (23.1 mg, 83% yield) **^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.39 (d, *J* = 2.2 Hz, 1H), 6.29 (d, *J* = 2.0 Hz, 1H), 4.38 – 4.28 (m, 1H), 3.90 (s, 3H), 3.84 (s, 3H), 2.92 – 2.72 (m, 2H), 1.88 – 1.75 (m, 1H), 1.70 – 1.59 (m, 1H), 1.57 – 1.47 (m, 1H), 1.46 – 1.37 (m, 1H), 1.34 – 1.26 (m, 4H), 0.88 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** 164.2, 163.0, 162.7, 143.9, 107.0, 103.8, 97.7, 77.2, 56.1, 55.4, 34.8, 34.6, 31.5, 24.6, 22.5, 13.9. **IR (KBr, ν / cm^{-1})** 2937, 2862, 1720, 1595, 1459, 1412, 1340, 1258, 1108, 851, 758. **HRMS (ESI, m/z):** calcd for $C_{16}H_{23}O_4^+$ [M + H]$^+$: 279.1591; found: 279.1594.

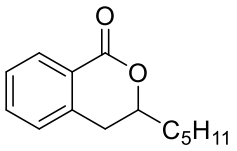


6,7,8-trimethoxy-3-pentylisochroman-1-one (9c): White solid (27.4 mg, 89% yield) **^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.49 (s, 1H), 4.40 – 4.31 (m, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 3.84 (s, 3H), 2.89 – 2.73 (m, 2H), 1.87 – 1.7 5 (m, 1H), 1.69 – 1.59 (m, 1H), 1.59 – 1.47 (m, 1H), 1.47 – 1.36 (m, 1H), 1.35 – 1.23 (m, 4H), 0.87 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 162.4, 157.3, 156.1, 141.8, 137.1, 111.8, 105.5, 77.6, 61.8, 61.1, 56.0, 34.6, 34.3, 31.5, 24.5, 22.4, 13.9. **IR (KBr, ν / cm^{-1})** 2935, 2862, 1720, 1604, 1584, 1463, 1340, 1161, 1041, 834. **HRMS (ESI, m/z):** calcd for $C_{17}H_{25}O_5^+$ [M + H]$^+$: 309.1697; found: 309.1694.



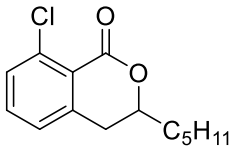
3-pentylisochroman-1-one (9d):

colorless oil (18.7 mg, 86% yield) **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.08 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.51 (td, *J* = 7.5, 1.4 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 4.57 – 4.45 (m, 1H), 3.02 – 2.84 (m, 2H), 1.92 – 1.82 (m, 1H), 1.76 – 1.64 (m, 1H), 1.62 – 1.40 (m, 2H), 1.37 – 1.29 (m, 4H), 0.93 – 0.85 (m, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.69, 139.23, 133.61, 130.23, 127.56, 127.34, 125.25, 78.77, 34.95, 33.22, 31.57, 24.60, 22.52, 13.99. **HRMS (ESI, m/z):** calcd for $C_{14}H_{19}O_2^+$ [M + H]$^+$: 219.1380; found: 219.1376.



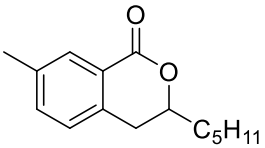
8-chloro-3-pentylisochroman-1-one (9e):

colorless oil (15.1 mg, 60% yield) **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.47 – 7.35 (m, 2H), 7.14 (dd, *J* = 6.5, 1.7 Hz, 1H), 4.49 – 4.35 (m, 1H), 3.03 – 2.84 (m, 2H), 1.92 – 1.78 (m, 1H), 1.75 – 1.63 (m, 1H), 1.63 – 1.51 (m, 1H), 1.50 – 1.41 (m, 1H), 1.35 – 1.27 (m, 4H), 0.90 (td, *J* = 6.9, 5.8, 3.0 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 162.12, 142.14, 136.56, 133.19, 130.87, 125.92, 123.23, 78.11, 34.60, 34.53, 31.50, 24.55, 22.50, 13.98. **HRMS (ESI, m/z):** calcd for $C_{14}H_{18}ClO_2^+$ [M + H]$^+$: 253.0990; found: 253.0994.



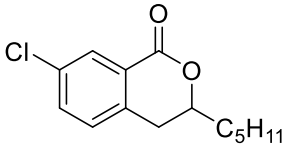
6-methyl-3-pentylisochroman-1-one (9f):

colorless oil (19.4 mg, 84% yield) **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.89 (s, 1H), 7.32 (d, *J* = 7.7 Hz, 1H), 7.11 (d, *J* = 7.7 Hz, 1H), 4.54 – 4.41 (m, 1H), 3.04 – 2.72 (m, 2H), 2.37 (s, 3H), 1.95 – 1.79 (m, 1H), 1.75 – 1.64 (m, 1H), 1.61 – 1.51 (m, 1H), 1.51 – 1.38 (m, 1H), 1.40 – 1.23 (m, 4H), 1.03 – 0.81 (m, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.9, 137.3, 136.2, 134.4, 130.4, 127.1, 124.9, 78.8, 34.9, 32.8, 31.5, 24.5, 22.4, 20.90, 13.9. **IR (KBr, ν / cm^{-1})** 3210, 2964, 1820, 1638, 1404, 1362, 1244, 1131, 832, 761. **HRMS (ESI, m/z):** calcd for $C_{15}H_{21}O_2^+$ [M + H]$^+$: 233.1536; found: 233.1535.



7-chloro-3-pentylisochroman-1-one (9g):

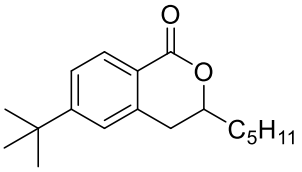
colorless oil (15.8 mg, 63% yield) **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.06 (d, *J* = 2.2 Hz, 1H),



7.48 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.19 (d, *J* = 8.1 Hz, 1H), 4.55 – 4.45 (m, 1H), 2.98 – 2.85 (m, 2H), 1.91 – 1.80 (m, 1H), 1.78 – 1.67 (m, 1H), 1.61 – 1.50 (m, 1H), 1.49 – 1.41 (m, 1H), 1.37 – 1.24 (m, 4H), 0.93 – 0.85 (m, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.43, 137.43, 133.61, 133.56, 130.00, 128.80, 126.68, 78.87, 34.83, 32.62, 31.50, 24.53, 22.48, 13.95. **HRMS (ESI, m/z):** calcd for $C_{14}H_{18}ClO_2^+$ $[M + H]^+$: 253.0990; found: 253.0984.

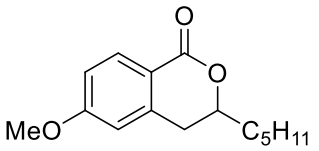
6-(tert-butyl)-3-pentylisochroman-1-one (9h):

colorless oil (23.8 mg, 87% yield) **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.01 (d, *J* = 8.2 Hz, 1H), 7.41 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.24 – 7.21 (m, 1H), 4.56 – 4.46 (m, 1H), 3.01 – 2.84 (m, 2H), 1.95 – 1.84 (m, 1H), 1.77 – 1.67 (m, 1H), 1.61 – 1.53 (m, 1H), 1.52 – 1.40 (m, 1H), 1.37 – 1.28 (m, 14H), 0.96 – 0.85 (m, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.79, 157.51, 139.03, 130.06, 124.79, 124.14, 122.52, 78.75, 35.15, 34.98, 33.55, 31.55, 31.02, 24.59, 22.50, 13.9. **HRMS (ESI, m/z):** calcd for $C_{18}H_{27}O_2^+$ $[M + H]^+$: 275.2006; found: 275.2014.



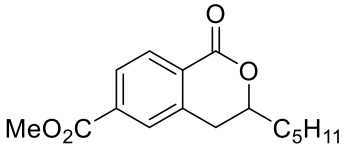
6-methoxy-3-pentylisochroman-1-one (9i):

colorless oil (22.3 mg, 90% yield) **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.03 (d, *J* = 8.6 Hz, 1H), 6.87 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.70 (d, *J* = 2.4 Hz, 1H), 4.53 – 4.44 (m, 1H), 3.86 (s, 3H), 2.98 – 2.81 (m, 2H), 1.92 – 1.80 (m, 1H), 1.74 – 1.66 (m, 1H), 1.62 – 1.54 (m, 1H), 1.49 – 1.43 (m, 1H), 1.38 – 1.27 (m, 4H), 0.95 – 0.87 (m, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ165.59, 163.68, 141.50, 132.47, 117.76, 113.34, 112.04, 78.40, 55.47, 34.90, 33.54, 31.54, 24.57, 22.48, 13.95. **HRMS (ESI, m/z):** calcd for $C_{15}H_{21}O_3^+$ $[M + H]^+$: 249.1485; found: 249.1474.



methyl 1-oxo-3-pentylisochromane-6-carboxylate (9j):

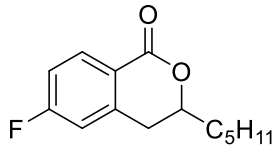
White solid (19.8 mg, 72% yield) **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.15 (d, *J* = 8.1 Hz, 1H), 8.01 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.94 – 7.91 (m, 1H), 4.59 – 4.49 (m, 1H), 3.95 (s, 3H), 3.03 – 2.96 (m, 2H), 1.95 – 1.84 (m, 1H), 1.79 – 1.68 (m, 1H), 1.59 – 1.51 (m, 1H), 1.49 – 1.42 (m, 1H), 1.36 – 1.30 (m, 4H), 0.95 – 0.87 (m, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.97, 164.76,



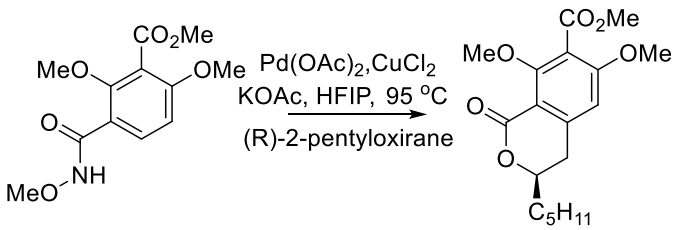
139.24, 134.42, 130.35, 128.81, 128.58, 128.42, 78.90, 52.56, 34.84, 33.08, 31.50, 24.55, 22.49, 13.96. **HRMS (ESI, m/z):** calcd for $C_{16}H_{21}O_4^+$ [M + H] $^+$: 277.1435; found: 277.1430.

6-fluoro-3-pentylisochroman-1-one (9k):

colorless oil (17.2 mg, 73% yield) **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.10 (dd, *J* = 8.7, 5.7 Hz, 1H), 7.05 (td, *J* = 8.6, 2.6 Hz, 1H), 6.93 (dd, *J* = 8.7, 2.5 Hz, 1H), 4.56 – 4.48 (m, 1H), 3.05 – 2.82 (m, 2H), 1.92 – 1.82 (m, 1H), 1.76 – 1.69 (m, 1H), 1.64 – 1.53 (m, 1H), 1.50 – 1.41 (m, 1H), 1.38 – 1.27 (m, 4H), 0.94 – 0.85 (m, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.71 (d, *J* = 256.0 Hz), 164.69, 142.22 (d, *J* = 9.4 Hz), 133.19 (d, *J* = 9.9 Hz), 121.55 (d, *J* = 2.9 Hz), 115.10 (d, *J* = 22.1 Hz), 114.17 (d, *J* = 22.2 Hz), 78.55, 34.82, 33.28, 31.49, 24.51, 22.46, 13.94. **^{19}F-NMR (376 MHz, $CDCl_3$)** δ -103.9. **HRMS (ESI, m/z):** calcd for $C_{14}H_{18}FO_2^+$ [M + H] $^+$: 237.1285; found: 237.1287.



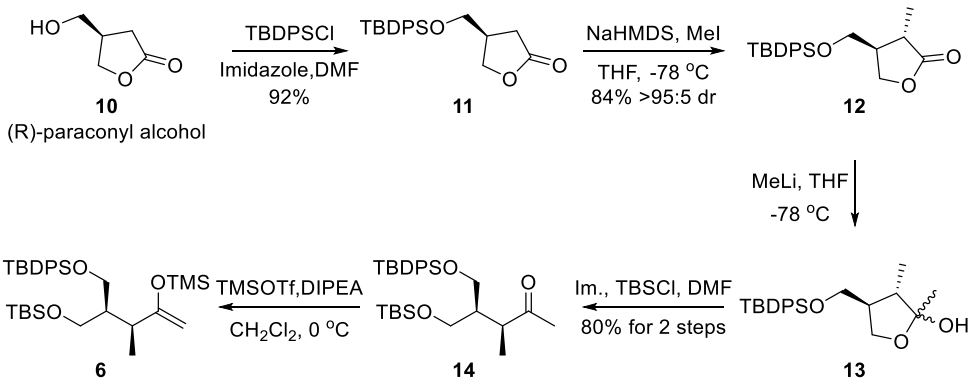
Procedure for gram-scale alkylation of 8a':



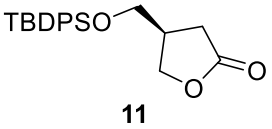
8a' 1.23g **(R)-9a** 1.15 g

A suspension of methyl 2,6-dimethoxy-3-(methoxycarbamoyl)benzoate (**8a'**) (1.21 g, 4.5 mmol), epoxide (*R*)-**7** (1.03 g, 9.0 mmol), KOAc (0.44 g, 4.5 mmol), $Pd(OAc)_2$ (50 mg, 0.23 mmol) $CuCl_2$ (120 mg, 0.9 mmol) and hexafluoroisopropanol (11.3 mL) in a sealed tube was stirred at 95 °C. After 48 hours, the reaction mixture was concentrated and purified by column chromatography (ethyl acetate: petroleum ether = 1:2) to give the product (*R*)-**9a** as a white solid. (1.13 g, 75% yield).

Procedure to prepare fragment 6

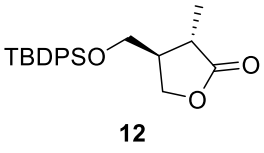


(*S*)-4-(((tert-butyldiphenylsilyl)oxy)methyl)dihydrofuran-2(3H)-one (11):



The imidazole (4.27 g, 62.8 mmol) and TBDPSCl (9.8 mL, 37.6 mmol) was added to the solution of the (*R*)-paraconyl alcohol[3] (3.64 g, 31.4 mmol) in DMF (31 mL) at room temperature under Argon. The reaction mixture was stirred at room temperature for 15 min (until starting material disappearance). then diluted with EtOAc, washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue so obtained was purified by flash column chromatography with ethyl acetate/petroleum ether (1:15) to afford the title compound **11** (10.2 g, 92%) as a colorless oil. $[\alpha]_D^{25}$ = +5.36 (c = 1.3 in $CHCl_3$)]. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.71 – 7.54 (m, 4H), 7.50 – 7.36 (m, 6H), 4.39 (dd, *J* = 9.1, 7.5 Hz, 1H), 4.23 (dd, *J* = 9.1, 5.5 Hz, 1H), 3.75 – 3.55 (m, 2H), 2.85 – 2.65 (m, 1H), 2.57 (dd, *J* = 17.6, 8.9 Hz, 1H), 2.41 (dd, *J* = 17.6, 6.2 Hz, 1H), 1.06 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 176.93, 135.45, 132.81, 132.78, 129.88, 127.78, 70.46, 64.07, 37.17, 30.72, 26.69, 19.15. **IR (KBr, ν / cm^{-1})** 2957, 2858, 1779, 1472, 1172, 1112, 823, 702. **HRMS (ESI, m/z):** calcd for $C_{21}H_{26}NaO_3Si^+$ $[M+Na]^+$: 377.1543; found: 377.1538.

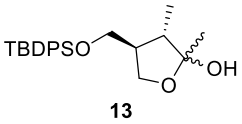
(3*S*,4*S*)-4-(((tert-butyldiphenylsilyl)oxy)methyl)-3-methyldihydrofuran-2(3H)-one (12):



NaHMDS (1.5 M in THF, 7.8 mL, 11.7 mmol) was added dropwise over 10 min to a solution of lactone **11** (3.5 g, 9.8 mmol) in THF (50 mL) at -78 °C under argon. The reaction mixture was stirred at

-78 °C for 30 min, and then methyl iodide (0.92 mL, 14.7 mmol) was added. The reaction mixture was stirred at -78 °C for a further 2 h and then quenched with saturated NH_4Cl solution (30 mL), warmed to room temperature, and extracted with EtOAc (3 × 50 mL). The combined organics were dried (Na_2SO_4) and concentrated in vacuo. The residue so obtained was purified by flash column chromatography with ethyl acetate/petroleum ether (1: 10) to afford the title compound **12** (3.03 g, 84%) as a pale yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.66 – 7.60 (m, 4H), 7.49 – 7.36 (m, 6H), 4.36 (m, 1H), 4.10 (t, *J* = 9.1 Hz, 1H), 3.76 (dd, *J* = 10.7, 4.2 Hz, 1H), 3.69 (dd, *J* = 10.7, 5.4 Hz, 1H), 2.66 – 2.45 (m, 1H), 2.41 – 2.25 (m, 1H), 1.18 (d, *J* = 7.1 Hz, 3H), 1.06 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 179.69, 135.43, 132.75, 132.71, 129.93, 129.90, 127.80, 127.78, 68.39, 62.18, 45.66, 36.09, 26.73, 19.17, 13.91. **IR (KBr, ν / cm^{-1})** 3073, 2933, 2860, 1779, 1589, 1472, 1112, 1015, 823, 702. **HRMS (ESI, m/z):** calcd for $C_{22}H_{28}NaO_3Si^+$ [M+Na] $^+$: 391.1700; found: 391.1704.

(3*S*,4*S*)-4-(((tert-butyldiphenylsilyl)oxy)methyl)-2,3-dimethyltetrahydrofuran-2-ol (13):

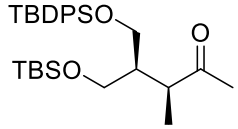


13

To a stirred solution of **12** (2.47 g, 6.70 mmol) in THF (67 mL) was added Methyllithium (1.5 M in diethyl ether, 5.36 mL, 8.04 mmol) at -78 °C under argon. After being stirred at the same temperature for 2 h, then quenched with saturated NH_4Cl solution (60 mL), warmed to room temperature, and extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with brine, filtered and dried over Na_2SO_4, and concentrated under reduced pressure to leave the residue, which was used directly in the next step.

(3*S*,4*S*)-5-((tert-butyldimethylsilyl)oxy)-4-(((tert-butyldiphenylsilyl)oxy)methyl)-3-methylpentan-2-one (14):

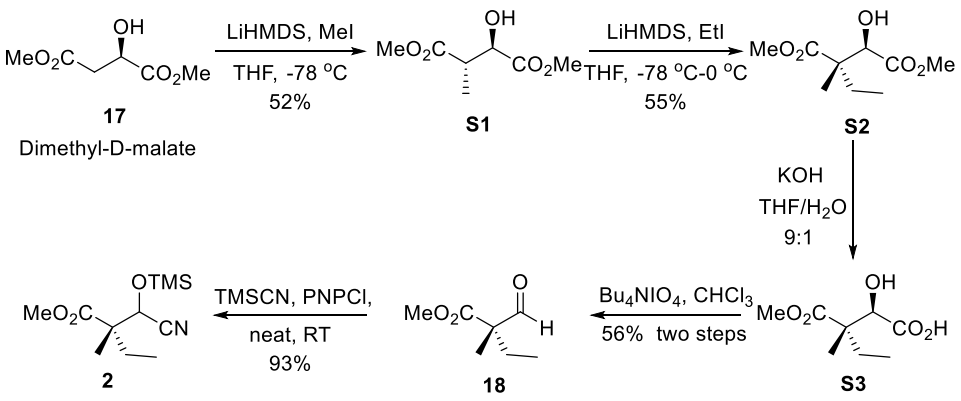
TBSCl (1.47 g, 9.75 mmol) was added to a solution of crude lactol **13** (~6.5 mmol) and imidazole (884 mg, 13.0 mmol) in dimethylformamide (6.5 mL) at room temperature under argon. The reaction mixture was stirred at room temperature for 4 h then diluted with EtOAc, washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by flash column chromatography with ethyl acetate/petroleum ether (1:



14

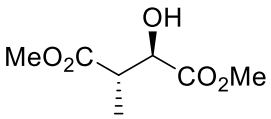
80) to afford the title compound **14** (2.67 g, 80% over two steps) as a pale yellow oil. $[\alpha]_D^{22}$ = -17.62 (c = 1.0 in $CHCl_3$)] **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.68 – 7.61 (m, 4H), 7.46 – 7.34 (m, 6H), 3.73 – 3.62 (m, 2H), 3.62 – 3.55 (m, 2H), 2.72 (p, *J* = 7.1 Hz, 1H), 2.14 (s, 3H), 2.12 – 2.06 (m, 1H), 1.04 (s, 9H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.87 (s, 9H), 0.02 (d, *J* = 1.9 Hz, 6H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 212.12, 135.54, 135.49, 133.46, 133.33, 129.58, 129.57, 127.59, 61.69, 61.11, 45.41, 45.14, 28.86, 26.74, 25.84, 19.14, 18.20, 12.67, -5.56, -5.58. **IR (KBr, ν / cm^{-1})** 3403, 2933, 2860, 1427, 1390, 1112, 1023, 998, 823, 702. **HRMS (ESI, m/z):** calcd for $C_{29}H_{46}NaO_3Si_2^+$ $[M+Na]^+$:521.2878; found: 521.2871.

Procedure to prepare the Fragment 2[4]



Dimethyl (2*R*,3*S*)-2-hydroxy-3-methylsuccinate (S1):

A solution of dimethyl D-malate (3.00 g, 18.5 mmol) in THF (5.0 mL) was added solution of LiHMDS (1.5 M in THF, 30.8 mL, 46.3 mmol) at –78 °C. After 1 h, MeI (1.15 mL, 18.5 mmol) was introduced and the reaction mixture was stirred at -78 °C for a further 12 h and then quenched with saturated NH_4Cl solution (30 mL), warmed to room temperature, and extracted with EtOAc (3 × 60 mL). The combined organics were dried (Na_2SO_4) and concentrated in vacuo. The residue so obtained was purified by flash column chromatography with ethyl acetate/petroleum ether (1: 2) to afford the title compound **S1** (1.69 g, 52%) as a colorless oil, The diastereoselectivity (anti:syn = 93:7) was determined by ^{1}H NMR. Major isomer (*anti*, 3S). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 4.27 (dd, *J* = 6.6, 3.6 Hz, 1H), 3.80 (s, 3H),

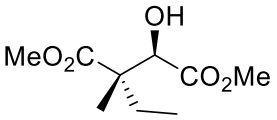


S1

3.69 (s, 3H), 3.16 (d, *J* = 6.5 Hz, 1H), 3.05 (qd, *J* = 7.3, 3.6 Hz, 1H), 1.30 (d, *J* = 7.3 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ173.65, 173.33, 72.35, 52.74, 52.01, 43.01, 13.07. **IR (KBr, ν / cm^{-1})** 3497, 2953, 1727, 1457, 1433 1203, 1112, 1063, 1008. **HRMS (ESI, m/z):** calcd for $C_7H_{13}O_5^+$ $[M+H]^+$: 177.0757; found: 177.0760.

Dimethyl (2*S*,3*R*)-2-ethyl-3-hydroxy-2-methylsuccinate (S2):

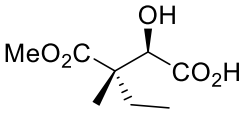
A solution of **S1** (1.60 g, 9.1 mmol) in THF (3.0 mL) was added solution of LiHMDS (1.5 M in THF, 13.3 mL, 20.0 mmol) at –78 °C. After 1.5 h, EtI (1.46 mL, 18.2 mmol) was introduced and the reaction mixture was stirred at -78 °C for a further 2 h before the mixture was warmed to 0 °C over the course of 13 h, then quenched with saturated NH_4Cl solution (20 mL), warmed to room temperature, and extracted with Et_2O (3 × 30 mL). The combined organics were dried (Na_2SO_4) and concentrated in vacuo. The residue so obtained was purified by flash column chromatography with ethyl acetate/petroleum ether (1: 3) to afford the title compound **S2** (1.02 g, 55%) as a colorless oil, The diastereoselectivity (anti:syn = 97:3) was determined by ^{1}H NMR. Major isomer (*anti*, 3R) **^{1}H NMR (400 MHz, $CDCl_3$)** δ 4.29 (d, *J* = 8.1 Hz, 1H), 3.78 (s, 3H), 3.72 (s, 3H), 3.37 (d, *J* = 8.1 Hz, 1H), 1.89 – 1.79 (m, 1H), 1.63 – 1.54 (m, 1H), 1.13 (s, 3H), 0.86 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ175.25, 173.26, 75.62, 52.46, 52.06, 50.57, 28.19, 16.53, 8.71. **IR (KBr, ν / cm^{-1})** 3500, 2959, 2880 1727, 1449, 1393, 1213, 1123, 1072, 980. **HRMS (ESI, m/z):** calcd for $C_9H_{17}O_5^+$ $[M+H]^+$: 205.1071; found: 205.1070.



S2

Methyl (S)-2-formyl-2-methylbutanoate (S3):

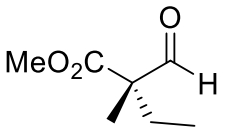
A mixture of **S2** (796 mg, 3.90 mmol) and KOH (437 mg, 7.8 mmol) in MeOH/water (9:1, 7.8 mL) was stirred for 3 h until TLC control indicated the completed consumption of the substrate. For work-up, water (10 mL) and Et_2O (30 mL) were added and the mixture was acidified to pH = 1 with aq. HCl (1 M). The aqueous phase was extracted with Et_2O (3 x 30 mL) and the combined organic phases were dried (Na_2SO_4) and evaporated to provide the title compound **S3** as a colorless oil, which was used directly in the next step.



S3

Methyl (S)-2-formyl-2-methylbutanoate (18):

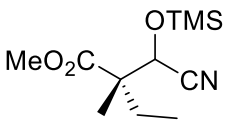
The tetrabutylammonium periodate (1.52 g, 3.5 mmol) is added and the solution of **S3** (~3.5 mmol) in $CHCl_3$ (7.0 mL), which is heated under reflux (65 °C) for 2 hours. After cooling the reaction, the solvent is removed under reduced pressure and the salts are precipitated in pentane, the combined organic phases were washed with aq. sat. $Na_2S_2O_3$ (2 x 10 mL) and brine (2 × 10 mL). The combined organics were dried (Na_2SO_4) and concentrated in vacuo. The residue so obtained was purified by flash column chromatography with ethyl acetate/petroleum ether (1: 10) to afford the title compound **18** (314.5 mg, 56% over two steps) as a colorless oil. $[\alpha]_D^{22}$ = -3.31 (c = 1.0 in $CHCl_3$) **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.71 (s, 1H), 3.76 (s, 3H), 2.01 – 1.90 (m, 1H), 1.83 – 1.72 (m, 1H), 1.28 (s, 3H), 0.88 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 199.81, 172.70, 58.04, 52.37, 27.32, 16.09, 8.61. **IR (KBr, ν / cm^{-1})** 2965, 2880, 2855, 1724, 1446, 1233, 1153, 1091. **HRMS (ESI, m/z):** calcd for $C_7H_{13}O_3^+$ $[M+H]^+$: 145.0859; found: 145.0863.



18

Methyl (2S)-2-(cyano((trimethylsilyl)oxy)methyl)-2-methylbutanoate (2):

The obtained aldehyde **20** (302 mg, 2.1 mmol), trimethylsylilcyanide (TMSCN) (248 mg, 2.5 mmol) and bis(triphenylphosporanylidene)ammonium chloride (PNPCl) (2 mg, 0.1 mol%) are added in Schlenk tube under argon flush. The mixture is then stirred at room temperature for 1 hour until disappearance of the starting material. The residue was purified by flash column chromatography with ethyl acetate/petroleum ether (1: 15) to afford the title compound **3** (475 mg, 93%) as a mixture of diastereoisomers (4:1) and as a colorless oil oil. **Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$)** δ 4.63 (s, 1H), 3.72 (s, 3H), 1.80 – 1.69 (m, 1H), 1.64 – 1.54 (m, 1H), 1.28 (s, 3H), 0.84 (t, *J* = 7.4 Hz, 3H), 0.20 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 173.66, 118.69, 65.92, 52.06, 51.37, 27.85, 17.25, 8.72, -0.58. **Minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$)** δ 4.74 (s, 1H), 3.68 (s, 3H), 1.80 – 1.69 (m, 1H), 1.64 – 1.54 (m, 1H),1.31 (s, 3H), 0.84 (t, *J* = 7.4 Hz, 3H), 0.17 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 173.33, 118.21, 67.68, 52.00, 51.37, 28.73, 15.26, 8.52, -0.65. **IR (KBr, ν / cm^{-1})**



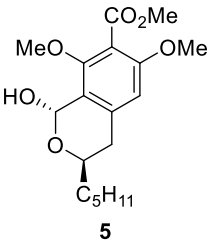
2

3012, 2890, 2254, 1733, 1446, 1254, 1101. **HRMS (ESI, m/z):** calcd for $C_{11}H_{22}NO_3Si^+$ $[M+H]^+$: 244.1363; found:244.1360.

Assembling of three fragments for synthesis of (-)-Berkelic acid.

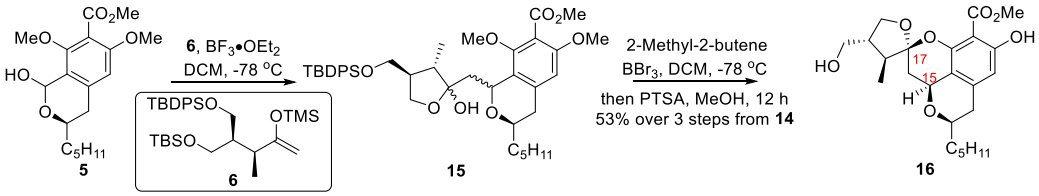
Methyl (3*R*)-1-hydroxy-6,8-dimethoxy-3-pentylisochromane-7-carboxylate (5):

DIBALH (1 M in toluene, 3.41 mL, 3.41 mmol) was added dropwise to a solution of lactone (R)-**9b** (954 mg, 2.84 mmol) in dichloromethane (19 mL) at -78 °C under argon. The reaction mixture was stirred at -78 °C with careful monitoring of the reaction to avoid over-reduction. For work-up, the methanol (1 mL) and saturated aqueous Rochelles' salt (20 mL) was added and stirred at room temperature for 3 h. The mixture was extracted with dichloromethane and the combined organics dried (Na_2SO_4) and concentrated. The crude product was purified by flash column chromatography with ethyl acetate/petroleum ether (1:5) to afford the title lactol **5** (691 mg, 72%) as a colorless oil: **^{1}H NMR (400 MHz, $CDCl_3$)** 6.42 (s, 1H), 6.10 (d, *J* = 3.3 Hz, 1H), 4.31 – 4.20 (m, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.80 (s, 3H), 3.03 (d, *J* = 3.1 Hz, 1H), 2.71 – 2.55 (m, 2H), 1.72 – 1.39 (m, 4H), 1.38 – 1.27 (m, 4H), 0.90 (t, *J* = 6.4 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ166.66, 156.94, 155.77, 138.59, 121.23, 115.52, 106.11, 88.44, 66.14, 62.63, 55.95, 52.50, 35.32, 34.09, 31.74, 24.94, 22.55, 14.00. **IR (KBr, ν / cm^{-1})** 3220, 2956, 1840, 1683, 1414, 1354, 1243, 1141, 842, 756. **HRMS (ESI, m/z):** calcd for $C_{18}H_{27}O_6^+$ $[M+H]^+$: 339.1802; found: 339.1807.



5

Methyl(2*S*,3*S*,3a'*S*,4*R*,5'*R*)-8'-hydroxy-4-(hydroxymethyl)-3-methyl-5'-pentyl-3',3a',4,5,5',6'-hexahydro-3H-spiro[furan-2,2'-pyrano[2,3,4-de]chromene]-9'-carboxylate (16):



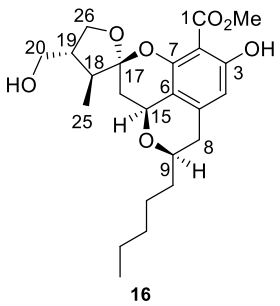
Fragment **6** was prepared following a slightly modified procedure described in literature.[4] TMSOTf (53 µL, 0.29 mmol) was added to a solution of methyl ketone **14** (95 mg, 0.19 mmol) and diisopropylethylamine (63 µL, 0.38 mmol) in dichloromethane (1 mL) at 0 °C

under argon. The reaction mixture was warmed to 25 °C and stirred for 1 h , For work-up, The reaction mixture was diluted with dichloromethane, washed with water, dried with Na_2SO_4, and concentrated in vacuo to afford **6** as a colorless oil, which was used directly in the next step as soon as possible.

$BF_3{\cdot}Et_2O$ (59 μL, 48% w/w, 0.24 mmol) was added dropwise to a solution of lactol **5** (67.6 mg, 0.2 mmol) in DCM (0.7 mL) at -78 °C under argon. The resulting yellow solution was stirred at -78 °C for 5 min and then warmed to 0 °C for futher 10 min. Then the reaction mixture was recooled to -78 °C and a solution of crude silyl enol ether **6** (~ 0.19 mmol) in DCM (0.7 mL) added. The resulting yellow solution was stirred at -78 °C for 1 h and then quenched with saturated aqueous $NaHCO_3$ (2 mL), warmed to room temperature, and extracted with DCM. The combined organics dried with Na_2SO_4, and concentrated in vacuo, the further purification by very flash column chromatography [ethyl acetate/petroleum ether (1: 4)] afforded the lactol **15** (113 mg), which was directly used in the next step.

BBr_3 (1.6 mol/L in dichloromethane, 250 μL, 0.4 mmol) was added dropwise to a solution of crude lactol **15** (113 mg, 0.16 mmol) and 2-Methyl-2-butene (41 μL, 0.48 mmol) in DCM (1.6 mL) at -78 °C under argon. The reaction mixture was stirred at that temperature for 2 h (until starting material disappearance). then quenched with MeOH (1 mL) and warmed to 25 °C, *p*-$TsOH{\cdot}H_2O$ (152 mg, 0.80 mmol,) in MeOH (4 mL) added, stirred for 12 h at ambient temperature before quenched with aqueous saturated $NaHCO_3$ solution (5 mL). The MeOH was removed in vacuo, the residue was diluted with water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with with brine, dried over Na_2SO_4, filtered, concentrated and evaporated under vacuum. The residue so obtained was purified by flash column chromatography (EtOAc/petroleum ether =1:1) to afford **16** (42 mg, 53% from **14**) as a yellow oil. $[\alpha]_D^{22}$ = -132.3 (c = 1.00 in $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.38 (s, 1H; OH), 6.32 (s, 1H; H_4), 4.76 (dd, *J* = 12.3, 5.4 Hz, 2H; H_{15}), 4.22 (t, *J* = 8.6 Hz, 1H; H_{26a}), 3.92 (s, 3H; MeO), 3.89 – 3.76 (m, 3H; H_9,H_{26b},H_{20a}), 3.74 – 3.66 (m, 1H; H_{20b}), 2.77 (dd, *J* = 17.4, 4.1 Hz, 1H; H_{8a}), 2.60 (dd, *J* =



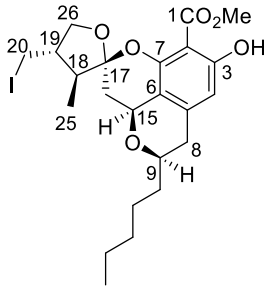
16

17.5, 11.0 Hz, 2H; H_{8b}), 2.56 – 2.47 (m, 1H; H_{19}), 2.20 (dd, *J* = 12.2, 5.4 Hz, 1H; H_{16eq}), 1.97 (t, *J* = 12.2 Hz, 1H; H_{16ax}), 1.93 – 1.86 (m, 1H; H_{18}).1.69-1.27 (m, 9H; H_{10}-H_{13}, OH_{20}). 1.12 (d, *J* = 6.7 Hz, 3H; H_{25}), 0.90 (t, *J* = 6.9 Hz, 3H; H_{14}). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.53, 162.05, 151.91, 141.32, 112.61, 109.45, 108.42, 99.90, 75.06, 70.00, 68.15, 63.69, 52.07, 46.19, 45.16, 36.30, 34.48, 33.57, 31.74, 25.05, 22.56, 14.00, 12.27. **IR (KBr, ν / cm^{-1})** 3220-3600, 2946, 2837, 1806, 1733, 1642, 1584, 1433, 1354, 1245, 1041, 824, 776. **HRMS (ESI, m/z):** calcd for $C_{23}H_{33}O_7^+$ $[M+H]^+$: 421.2221; found:421.2215.

Methyl(2S,3S,3a'S,4S,5'R)-8'-hydroxy-4-(iodomethyl)-3-methyl-5'-pentyl-3',3a',4,5,5',6'-hexahydro-3H-spiro[furan-2,2'-pyrano[2,3,4-de]chromene]-9'-carboxylate (3):

Iodide **3** was prepared following a slightly modified procedure described in literature.[4] A solution of iodine (46 mg, 0.18 mmol) in Et_2O: MeCN=3:1 (0.6 mL) was added dropwise to a solution of compound **16** (67.2 mg, 0.16 mmol), PPh_3 (47 mg, 0.18 mmol) and imidazole (33 mg, 0.48 mmol) in Et_2O: MeCN=3:1 (1 mL). The mixture was stirred for 30 min before being quenched with aqueous saturated $Na_2S_2O_3$ solution (1 mL) and the aqueous layer is extracted with ethyl acetate (5 mL × 3), dried (Na_2SO_4), filtered and evaporated. Purification of the residue by flash chromatography (EtOAc/petroleum ether = 1:10) afforded iodide **3** as a white solid (76 mg, 90 %); Suitable crystals for crystallographic analysis were obtained from crystallization in EtOH/DCM. $[\alpha]_D^{22.7}$ = -46.5 (c = 0.005 in $CHCl_3$). **CCDC** 2004145 contains the supplementary crystallographic data of **3**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.38 (s, 1H; OH), 6.32 (s, 1H; H_4), 4.75 (dd, *J* = 12.3, 5.4 Hz, 1H; H_{15}), 4.22 (t, *J* = 8.5 Hz, 1H; H_{26a}), 3.93 (s, 3H; MeO), 3.85 – 3.76 (m, 1H; H_9), 3.69 (t, *J* = 8.2 Hz, 1H; H_{26b}), 3.43 (dd, *J* = 9.9, 3.8 Hz, 1H; H_{20a}), 3.21 – 3.14 (m, 1H; H_{20b}), 2.76 (dd, *J* = 17.5, 4.0 Hz, 1H; H_{8a}), 2.60 (dd, *J* = 17.6, 11.1 Hz, 1H; H_{8b}), 2.65 – 2.46 (m, 1H; H_{19}), 2.22 (dd, *J* = 12.2, 5.4 Hz, 1H; H_{16eq}), 1.93 (t, *J* = 12.2 Hz, 1H; H_{16ax}),



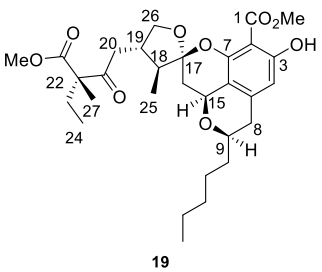
3

1.82 (dq, *J* = 10.3, 6.6 Hz, 1H; H_{18}), 1.69 – 1.26 (m, 8H; H_{10}-H_{13}), 1.09 (d, *J* = 6.7 Hz, 3H; H_{25}), 0.90 (t, *J* = 6.8 Hz, 3H; H_{14}). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.41, 162.03, 151.64, 141.33, 112.47, 109.86, 108.55, 99.81, 75.06, 73.52, 67.88, 52.15, 49.50, 45.94, 36.27, 34.43, 33.64, 31.73, 25.05, 22.56, 14.02, 11.61, 7.53. **IR (KBr, ν / cm^{-1})** 3508, 2996, 1864, 1693, 1436, 1346, 1248, 1194, 1148, 876, 768, 524. **HRMS (ESI, m/z):** calcd for $C_{23}H_{32}IO_6^+$ $[M+H]^+$: 531.1238; found: 531.1232.

Methyl(2S,3S,3a'S,4S,5'R)-8'-hydroxy-4-((S)-3-(methoxycarbonyl)-3-methyl-2-oxopentyl)-3-methyl-5'-pentyl-3',3a',4,5,5',6'-hexahydro-3H-spiro[furan-2,2'-pyrano[2,3,4-de]chromene]-9'-carboxylate (19):

To a stirred solution of fragment **2** (21.0 mg, 0.086 mmol.) in THF (0.4 mL) was added LDA (2.0 mol/L in THF, 0.065 mL, 0.13 mmol.) at -78 °C under argon atmosphere. After being stirred at the same temperature for 1h, another portion of LDA (2.0 mol/L in THF, 0.043 mL, 0.086 mmol) and DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone) (0.024 mL, 0.2 mmol) was added and stirred for 2 minutes. Iodide **3** (41.4 mg, 0.078 mmol) in THF (0.2 mL) was added. The resulting mixture was slowly warmed to -60 °C stirred for 30 minutes. After being quenched with saturated aqueous NH_4Cl solution, the organic layer was separated and the aqueous layer extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine, filtered and dried over Na_2SO_4, concentrated under reduced pressure to leave the residue, which was dissolved into 0.6 mL of methanol and tetrabutylammoniumfluoride (1.0 mol/L in THF, 0.17 mL, 0.17 mmol) is added at 0°C and the reaction mixture is stirred for 3 hours. The reaction is quenched with saturated aqueous solution of NH_4Cl (5 mL) and the aqueous layers are extracted with ethyl acetate (3 ×5 mL). The combined organic layers are dried (Na_2SO_4), filtered and evaporated. The residue was purified by column chromatography (EtOAc/petroleum ether =1:10) to give diester **19** (36.6 mg, 86%). $[\alpha]_D^{22}$ = -49.0 (c = 0.03 in $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.40 (s, 1H; OH), 6.31 (s, 1H; H_4), 4.75 (dd, *J* = 12.1, 5.0 Hz, 1H; H_{15}), 4.33 (t, *J* = 8.5 Hz,



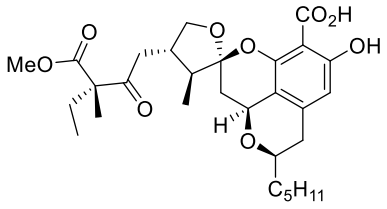
19

1H; H_{26a}), 3.95 (s, 3H; $C_{28}OOMe$), 3.84 – 3.78 (m, 1H; H_9), 3.75 (s, 3H; C_1OOMe), 3.46 (t, *J* = 8.2 Hz, 1H; H_{26b}), 2.81 – 2.72 (m, 3H; H_{20a}, H_{20b}, H_{19}), 2.60 (dd, *J* = 17.4, 10.9 Hz, 1H; H_{8a}), 2.45 (dd, *J* = 18.2, 10.8 Hz, 1H; H_{8b}), 2.16 (dd, *J* = 12.1, 5.3 Hz, 1H; H_{16eq}), 2.02 – 1.97 (m, 1H; H_{23a}), 1.97 – 1.92 (m, 1H; H_{16ax}), 1.90 – 1.78 (m, 1H; H_{23b}), 1.74-1.47 (m, 4H; H_{18}, H_{10}, H_{11a}), 1.37 –1.28(m, 5H; H_{11b}, H_{12}, H_{13}), 1.34(s, 3H; H_{27}), 1.04 (d, *J* = 6.6 Hz, 3H; H_{25}), 0.92 – 0.88 (m, 3H; H_{14}), 0.85 (t, *J* = 7.6 Hz, 3H; H_{24}). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 206.75, 173.38, 171.54, 162.04, 151.86, 141.17, 112.46, 108.57, 108.36, 99.93, 75.06, 72.81, 68.07, 59.80, 52.37, 52.13, 48.22, 41.61, 38.86, 36.28, 34.44, 33.60, 31.73, 27.82, 25.04, 22.56, 18.35, 14.00, 11.55, 8.62. **IR (KBr, ν / cm^{-1})** 3025, 2953, 2856, 1740, 1707, 1653, 1604, 1414, 1300, 1243, 1207, 1041, 806. **HRMS (ESI, m/z):** calcd for $C_{30}H_{43}O_9^+$ $[M+H]^+$: 547.2902; found: 547.2900.

(–)-Berkelic acid (1):

Selective hydrolysis of aromatic carboxylic acid was referred to a previously reported literature.[5] $(Bu_3Sn)_2O$ (21.8 mg, 0.036 mmol) was added to a solution of the diester **19** (20 mg, 0.036 mmol) in toluene (0.3 mL) in an Ar-purged Schlenk tube; and heated to 115 °C. After 7 h the yellow reaction was cooled to room temperature, diluted with CH_3CN (2 mL) and 1M HCl (5 mL), stirred vigorously for 15 min, and the resultant mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated. The resultant material was purified by semi-preperative HPLC purification (reversed phase, 20 × 250 mm; mobile phase: methanol: water (0.1% Formic acid) = 9:1, The detection wavelengths were 210 nm and 235 nm) to give **27** (10.5 mg, 55%) as a white solid. $[\alpha]_D^{22}$ = -83.71 (c = 0.05 in MeOH).

^{1}H NMR (400 MHz, $CDCl_3$ δ 7.24 ppm**)** δ 11.82 (s, 1H; OH), 11.01 (br s, 1H; COOH), 6.42 (s, 1H; H_4), 4.77 (dd, *J* = 12.1, 5.3 Hz, 1H; H_{15}), 4.44 (t, *J* = 8.7 Hz, 1H; H_{26a}), 3.86 – 3.75 (m, 1H; H_9), 3.73 (s, 3H; OCH_3), 3.63 – 3.55 (m, 1H; H_{26b}), 2.85 (dd, *J* = 16.9, 2.8 Hz, 1H; H_{20}), 2.78 (dd, *J* = 17.6, 4.1 Hz, 1H; H_{8a}), 2.60 (dd, *J* = 17.6, 11.0 Hz, 1H; H_{8b}), 2.54 – 2.47 (m, 1H; H_{19}),



(-)-Berkelic acid (1)

2.42 (dd, *J* = 16.8, 10.0 Hz, 1H; H_{20}), 2.21 (dd, *J* = 12.4, 5.3 Hz, 1H; H_{16a}), 2.06 (app t, *J* =

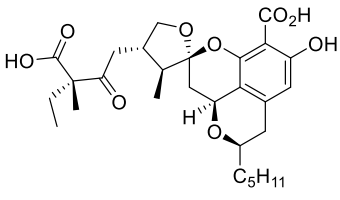
12.3 Hz, 1H; H_{16b}), 1.96 (dq, *J* = 14.9, 7.5 Hz, 1H; H_{23a}), 1.90 – 1.86 (m, 1H; H_{18}), 1.80 (dq, *J* = 14.8, 7.5 Hz, 1H; H_{23b}). 1.68 – 1.59 (m, 1H; H_{10a}), 1.58 – 1.41 (m, 3H; H_{10b}, H_{11}), 1.35 – 1.27 (m, 4H; H_{12}, H_{13}), 1.32 (s, 3H; H_{27}), 1.09 (d, *J* = 6.8 Hz, 3H; H_{25}), 0.88 (t, *J* = 6.9 Hz, 3H; H_{14}), 0.83 (t, *J* = 7.5 Hz, 3H; H_{24}). **^{13}C NMR (101 MHz, $CDCl_3$** δ 77.0 ppm) δ 206.00 (C21), 173.35 (C28), 170.47 (C1), 162.56 (C3), 149.78 (C3), 142.21 (C5), 112.20 (C6), 112.19 (C17), 110.51(C4), 98.66 (C2), 75.22 (C9), 73.53 (C26), 67.26 (C15), 59.78(C22), 52.47(OMe), 48.24(C18), 41.58(C20), 39.40(C19), 36.27(C10), 34.34(C8), 34.34 (C16), 31.77 (C12), 27.95 (C23), 25.03 (C11), 22.59 (C13), 18.43 (C27), 14.03 (C14), 12.00 (C25), 8.68 (C24). **IR (KBr, ν / cm^{-1})** 3230, 2944, 2857, 1740, 1713, 1684, 1554, 1463, 1243, 1179, 1006, 942, 863, 796. **HRMS (ESI, m/z):** calcd for $C_{29}H_{41}O_9^+$ $[M+H]^+$: 533.2745; found: 533.2739. The reported data are consistent with those previously reported.[5]

des-C28-carboxymethyl-Berkelic Acid (21):

To a solution of (–)-Berkelic acid (**1**) (13.8 mg, 0.026 mmol) in MeOH 1 mL at 0°C was slowly added aqueous KOH (1M, 0.052 mL, 0.052 mmol) over 15 min. The reaction mixture was allowed to warm to room temperature overnight with stirring. The combined aqueous extract was acidified to pH 2 with 1N HCl. The aqueous phase was extracted with Et_2O (three times). The combined organic extract was dried over $MgSO_4$ and purified by column chromatography to afford the desired acid **20** (1.6 mg, 12%) consistent with des-methyl carboxy-berkelic acid **21** (9.2 mg, 74%, ~1:1 mixture of C-22 diastereomers) as a white solid.

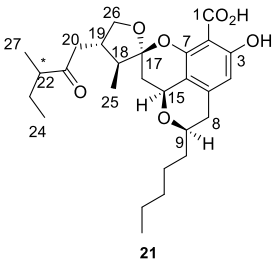
Diacid 20:

Diagnostic proton resonances: ^{1}H NMR (400 MHz, $CDCl_3$) 11.84 (s, 1H), 6.44 (s, 1H), 4.84 – 4.74 (m, 1H), 4.52 – 4.42 (m, 1H), 3.88 – 3.77 (m, 1H), 3.66 – 3.56 (m, 1H), 3.06 – 2.89 (m, 1H), 2.80 (m, 1H), 2.70 – 2.59 (m, 1H), 2.58 – 2.39 (m, 2H), 2.15 – 2.04 (m, 2H), 1.59-1.48 (m, 2H), 1.11 (m, 3H), 0.90 (m, 6H). **HRMS (ESI, m/z):** calcd for $C_{28}H_{38}NaO_9^+$ $[M+Na]^+$: 541.2408; found: 541.2403.



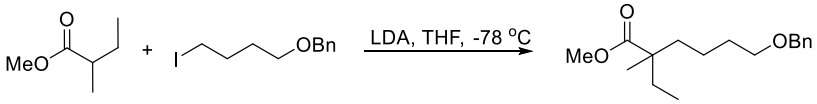
20

***des*-C28-carboxymethyl-Berkelic Acid (21):** 1:1 mixture of C-22 diastereomers, **^{1}H NMR (400 MHz, $CDCl_3$)** δ 11.87 (s, 1H), 11.10 (s, 1H), 6.44 (s, 1H), 4.79 (dd, *J* = 12.2, 5.3 Hz, 1H), 4.50 (td, *J* = 8.6, 5.6 Hz, 1H), 3.88 – 3.76 (m, 1H), 3.58 (ddd, *J* = 9.7, 8.0, 1.9 Hz, 1H), 2.92 (ddd, *J* = 17.1, 14.4, 2.8 Hz, 1H), 2.81 (dd, *J* = 17.6, 4.1 Hz, 1H), 2.62 (dd, *J* = 17.7, 11.0 Hz, 1H), 2.55 – 2.39 (m, 3H), 2.23 (dd, *J* = 12.4, 5.3 Hz, 1H), 2.08 (t, *J* = 12.3 Hz, 1H), 1.90 (dq, *J* = 10.7, 6.8 Hz, 1H), 1.74 – 1.61 (m, 2H), 1.59 – 1.46 (m, 2H), 1.41 (dtd, *J* = 14.0, 7.3, 3.1 Hz, 2H), 1.36 – 1.27 (m, 4H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.09 (d, *J* = 6.9 Hz, 3H), 0.88 (m, 6H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 212.60, 170.47, 162.40, 149.73, 142.13, 112.12, 112.08, 110.37, 98.53, 75.14, 73.63, 67.20, 48.19, 47.71, 47.61, 44.26, 44.04, 38.96, 38.88, 36.17, 34.24, 34.20, 31.69, 25.96, 25.83, 24.98, 22.55, 15.91, 15.72, 14.01, 12.00, 11.67, 11.57. **IR (KBr, ν / cm^{-1})** 3223, 2934, 2862, 1867, 1744, 1648, 1582, 1463, 1233, 1109, 1016, 942, 869. **HRMS (ESI, m/z):** calcd for $C_{27}H_{39}O_7^+$ $[M+H]^+$: 475.2690; found: 475.2688.



21

methyl 6-(benzyloxy)-2-ethyl-2-methylhexanoate (23):



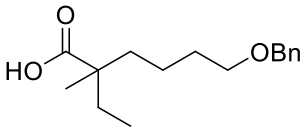
23

To a stirred solution of methyl 2-methylbutanoate (109 mg, 0.94 mmol.) in THF (4.7 mL) was added LDA (2.0 mol/L in THF, 0.71 mL, 1.41 mmol.) at -78 °C under argon atmosphere. After being stirred at the same temperature for 1 h, ((4-iodobutoxy)methyl)benzene (290 mg, 1 mmol) in THF (0.7 mL) was added. The resulting mixture was slowly warmed to -60 °C stirred for 30 minutes. After being quenched with saturated aqueous NH_4Cl solution, the organic layer was separated and the aqueous layer extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, filtered and dried over Na_2SO_4, concentrated under reduced pressure to leave the residue, The residue was purified by column chromatography (EtOAc/petroleum ether =1:10) to give **23** (212 mg, 81%) as a colorless oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.37 – 7.26 (m, 5H), 4.49 (s, 2H), 3.65 (s, 3H), 3.45 (t, *J* = 6.6 Hz, 2H), 1.69 – 1.56 (m, 4H), 1.50 – 1.32 (m, 3H), 1.26 – 1.15 (m, 1H), 1.11 (s, 3H), 0.81 (t,

J = 7.5 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ177.85, 138.53, 128.27, 127.55, 127.41, 72.82, 70.10, 51.42, 46.27, 38.72, 31.90, 30.15, 21.24, 20.59, 8.89. **HRMS (ESI, m/z):** calcd for $C_{17}H_{26}NaO_3^+$ $[M+Na]^+$: 301.1774; found: 301.1772.

6-(benzyloxy)-2-ethyl-2-methylhexanoic acid (22):

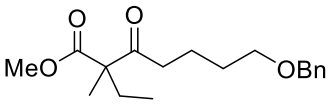
To a solution of **23** (200 mg, 0.72 mmol) in MeOH: H_2O = 3:1 (6 mL) was added KOH (80.6 mg, 1.44 mmol). The reaction mixture was allowed to reflux overnight with stirring. For work-up, the mixture was acidified to pH 1 with 1N HCl and the aqueous phase was extracted with DCM:MeOH= 15:1 (three times). The combined organic extract was dried over $MgSO_4$ and purified by column chromatography (AcOH: MeOH: DCM = 1:10:200) to afford the desired acid **22** (95 mg, 50%) as a colorless oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ7.37 – 7.25 (m, 5H), 4.50 (s, 2H), 3.46 (t, *J* = 6.6 Hz, 2H), 1.74 – 1.57 (m, 4H), 1.54 – 1.37 (m, 3H), 1.36 – 1.24 (m, 1H), 1.13 (s, 3H), 0.87 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ183.47, 138.52, 128.29, 127.60, 127.44, 72.85, 70.07, 46.02, 38.32, 31.61, 30.15, 21.16, 20.47, 8.82. **HRMS (ESI, m/z):** calcd for $C_{16}H_{24}NaO_3^+$ $[M+Na]^+$: 287.1618; found: 287.1614.



22

Methyl 7-(benzyloxy)-2-ethyl-2-methyl-3-oxoheptanoate (26):

To a stirred solution of fragment **2** (200.0 mg, 0.81 mmol) in THF (4 mL) was added LDA (2.0 mol/L in THF, 0.61 mL, 1.23 mmol) at -78 °C under argon atmosphere. After being stirred at the same temperature for 1h. ((4-iodobutoxy)methyl)benzene (258.1 mg, 0.89 mmol) in THF (2 mL) was added. The resulting mixture was slowly warmed to -60 °C stirred for 30 minutes. After being quenched with saturated aqueous NH_4Cl solution, the organic layer was separated and the aqueous layer extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, filtered and dried over Na_2SO_4, concentrated under reduced pressure to leave the residue, which was dissolved into 6 mL of methanol and tetrabutylammoniumfluoride (1.0 mol/L in THF, 1.62 mL, 1.62 mmol) is added at 0°C and the reaction mixture is stirred for 3 hours. The reaction is quenched with saturated aqueous solution of NH_4Cl (10 mL) and the aqueous layers are extracted with ethyl acetate (3 ×15 mL). The combined organic layers are dried (Na_2SO_4), filtered and evaporated. The residue was purified by column chromatography (EtOAc/petroleum ether =1:10) to give **26** (206 mg, 83%)

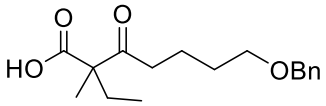


26

as a yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.37 – 7.26 (m, 5H), 4.49 (s, 2H), 3.69 (s, 3H), 3.46 (t, *J* = 6.2 Hz, 2H), 2.45 (td, *J* = 7.0, 3.6 Hz, 2H), 1.99 – 1.88 (m, 1H), 1.86 – 1.74 (m, 1H), 1.72 – 1.63 (m, 2H), 1.62 – 1.54 (m, 2H), 1.30 (s, 3H), 0.81 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 207.66, 173.68, 138.52, 128.36, 127.63, 127.53, 72.93, 70.05, 59.93, 52.24, 38.03, 29.11, 27.77, 20.63, 18.32, 8.64. **HRMS (ESI, m/z):** calcd for $C_{18}H_{26}NaO_4^+$ $[M+Na]^+$: 329.1723; found: 329.1725.

7-(benzyloxy)-2-ethyl-2-methyl-3-oxoheptanoic acid (25):

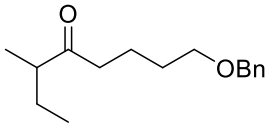
To a solution of **26** (100 mg, 0.32 mmol) in MeOH: H_2O = 3:1 (3 mL) was added KOH (26.9 mg, 0.48 mmol). The reaction mixture was stirring overnight at room temprature. For work-up, the mixture was acidified to pH 1 with 1N HCl and the aqueous phase was extracted with EtOAc (three times). The combined organic extract was dried over $MgSO_4$ and purified by column chromatography (AcOH: MeOH: DCM =1:10:100) to afford the desired acid **25** (81.3 mg, 87%) as a colorless oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.38 – 7.26 (m, 5H), 4.49 (s, 2H), 3.47 (t, *J* = 6.2 Hz, 2H), 2.55 (td, *J* = 6.9, 1.5 Hz, 2H), 1.98 – 1.80 (m, 2H), 1.73 – 1.65 (m, 2H), 1.64 – 1.56 (m, 2H), 1.35 (s, 3H), 0.86 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 208.33, 177.88, 138.29, 128.31, 127.63, 127.51, 72.86, 69.95, 59.56, 37.98, 28.93, 28.17, 20.45, 18.54, 8.69. **HRMS (ESI, m/z):** calcd for $C_{17}H_{24}NaO_4^+$ $[M+Na]^+$: 315.1567; found: 315.1569.



25

8-(benzyloxy)-3-methyloctan-4-one (27):

To a solution of **25** (50 mg, 0.17 mmol) in $CHCl_3$ (1 mL) in an Ar-purged Schlenk tube; and heated to 60 °C for 3 h. The mixture was concentrated under reduced pressure to leave the residue and purified by column chromatography (EtOAc/petroleum ether =1:10) to afford **27** (39.2 mg, 93%) as a colorless oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.38 – 7.26 (m, 5H), 4.50 (s, 2H), 3.47 (t, *J* = 6.1 Hz, 2H), 2.51 – 2.39 (m, 3H), 1.71 – 1.59 (m, 5H), 1.43 – 1.30 (m, 1H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.86 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 214.60, 138.49, 128.29, 127.58, 127.45, 72.86, 70.03, 47.78, 40.78, 29.25, 25.88, 20.39, 15.85, 11.65. **HRMS** (ESI, m/z): calcd for $C_{16}H_{25}O_2^+$ $[M+H]^+$: 249.1849; found: 249.1852.



27

References:

1. T. N. Snaddon, P. Buchgraber, S. Schulthoff, C. Wirtz, R. Mynott, A. Fürstner, *Chem.-Eur. J.* **2010**, *16*, 12133.

2. G. Cheng, T.-J. Li, J.-Q. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 10950.

3. A, M. Sarkale, A. Kumar, C. Appayee. *J. Org. Chem.* **2018**, *83*, 4167.

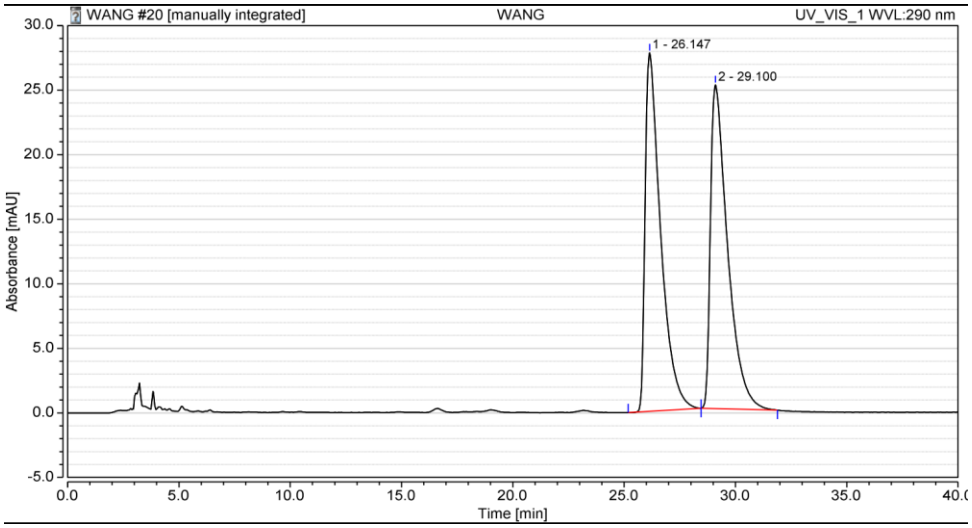
4.. J. Fañanás, A. Mendoza, T. Arto, B. Temelli, F. Rodríguez, *Angew. Chem. Int. Ed.* **2012**, *51*, 4930.

5. F. Bender, F. K. Yoshimoto, C. L. Paradise, Jef K. De Brabander, *J. Am. Chem. Soc.* **2009**, *131*, 11350.

3. HPLC Data of Compound (*R*)-9a

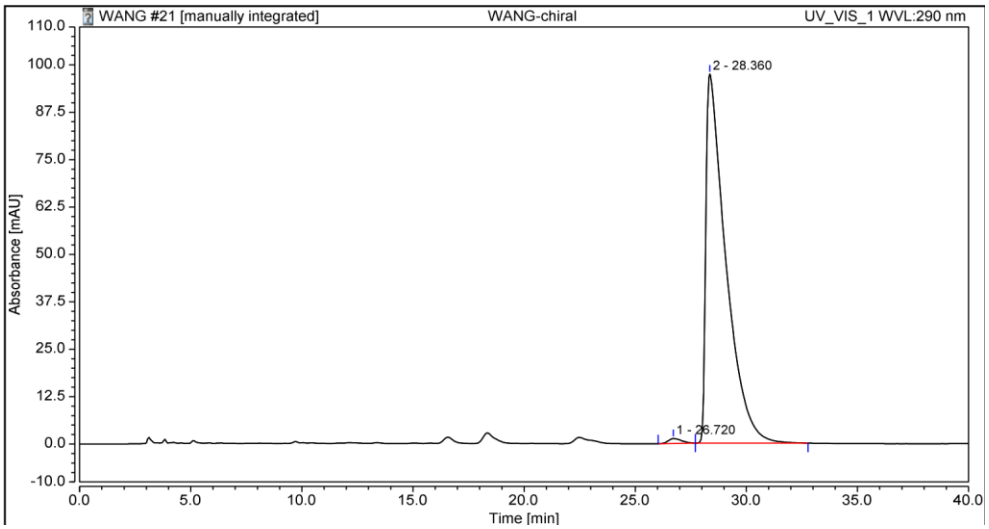
The enantiomeric excess of (R)-**9a** was determined to be 98% ee by HPLC [chiral column: CHIRALPAK AD-H; solvent: hexane/2-propanol = 40/1; flow rate: 0.4 mL/min; detection: at 290 nm, t_R ((R)-major)= 28.3 min, t_R ((S)-minor)= 26.2 min]

Chiral HPLC traces of RACE **9a**



Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		26.147	22.368	27.773	50.02	52.55	n.a.
2		29.100	22.350	25.082	49.98	47.45	n.a.
Total:			**44.717**	**52.854**	**100.00**	**100.00**	

Chiral HPLC traces of **(R)-9a**



Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		26.720	0.904	1.317	0.89	1.33	n.a.
2		28.360	100.976	97.370	99.11	98.67	n.a.
Total:			**101.880**	**98.687**	**100.00**	**100.00**	

4. Crystal Data and Structure Refinement for Compound 3

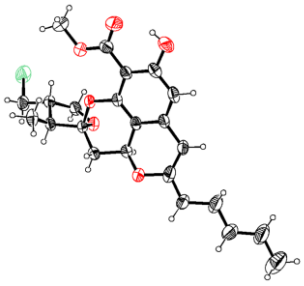
Experimental: Single crystals of $C_{23}H_{27}IO_6$ were obtained by recrystallization from mixed solvents of dichloromethane and ethanol. A suitable crystal was selected and carried out on a SuperNova, Dual, Cu at zero, Eos diffractometer. The crystal was kept at 296 K during data collection. Using Olex2,[1] the structure was solved with the ShelXS[2] structure solution program using Direct Methods and refined with the ShelXL[3] refinement package using Least Squares minimisation.

[1] Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.

[2] Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.

[3] Sheldrick, G.M. (2015). Acta Cryst. C71, 3-8.

Crystal Data:



Bond precision: C-C = 0.0097 A Wavelength=0.71073

Cell: a=14.34200 b=9.69100 c=18.13900

alpha=90 beta=107.5200 gamma=90

Temperature: 296 K

	Calculated	Reported
Volume	2404.160	2404
Space group	P 21/n	P 21/n
Hall group	-P 2yn	-P 2yn
Moiety formula	C23 H27 I O6	?
Sum formula	C23 H27 I O6	C23 H27 I O6
Mr	526.35	526.34
Dx, g cm-3	1.454	1.454
Z	4	4
Mu (mm-1)	1.365	1.365
F000	1064.0	1064.0
F000'	1062.60	
h, k, lmax	17, 11, 21	17, 11, 21
Nref	4242	4169
Tmin, Tmax	0.728, 0.761	0.589, 0.746
Tmin'	0.657	

Correction method= # Reported T Limits: Tmin=0.589 Tmax=0.746 AbsCorr = MULTI-SCAN

Data completeness= 0.983 Theta(max)= 24.998

R(reflections)= 0.0670(2675) wR2(reflections)= 0.2140(4169)

S = 1.003 Npar= 275

5. In vitro cytotoxicity assay:

To explore the cytotoxicity of compounds **1**, **19**, **21**, several cancer cell lines (**HCT-116**, **MGC-803**, **HUH-7**, **SGC-7901**) were chosen in cell viability test with MTT method. Cells in logarithmic phase were collected and plated in 96-well microtiter plates at a density of 5×104/well and incubated in a humidified atmosphere at 37 ℃ with 5% CO_2 for 24 h. Tested compounds of indicated concentrations (1.56, 3.13, 6.25, 12.5, 25, 50 μM) were added into triplicate wells with 0.1% DMSO added into control wells. After incubation for 24 h, 10 μL of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) solution (5 mg/mL) was added into each well, and the plates were incubated for 4 h. Disposing of culture medium and using DMSO (100 μL) to dissolve formazan crystals before final absorbance determination. All experiments were performed three times.

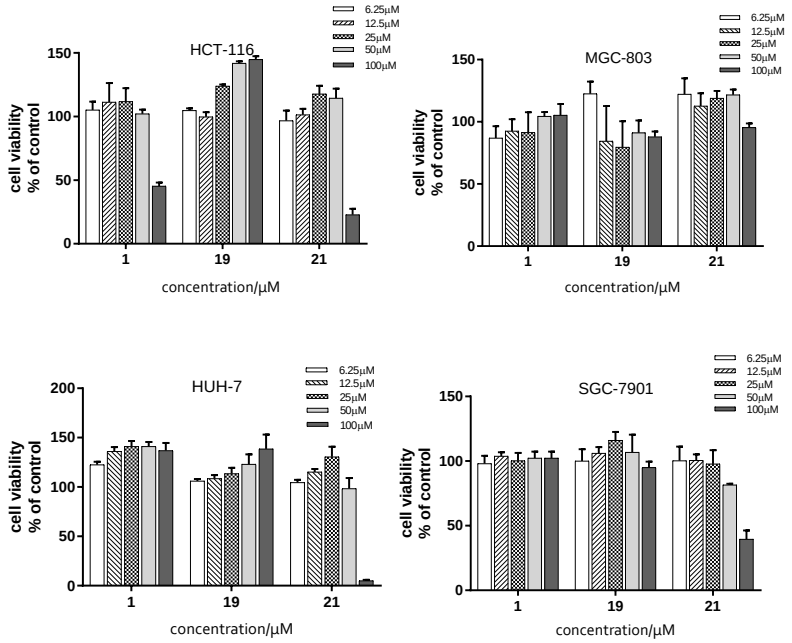
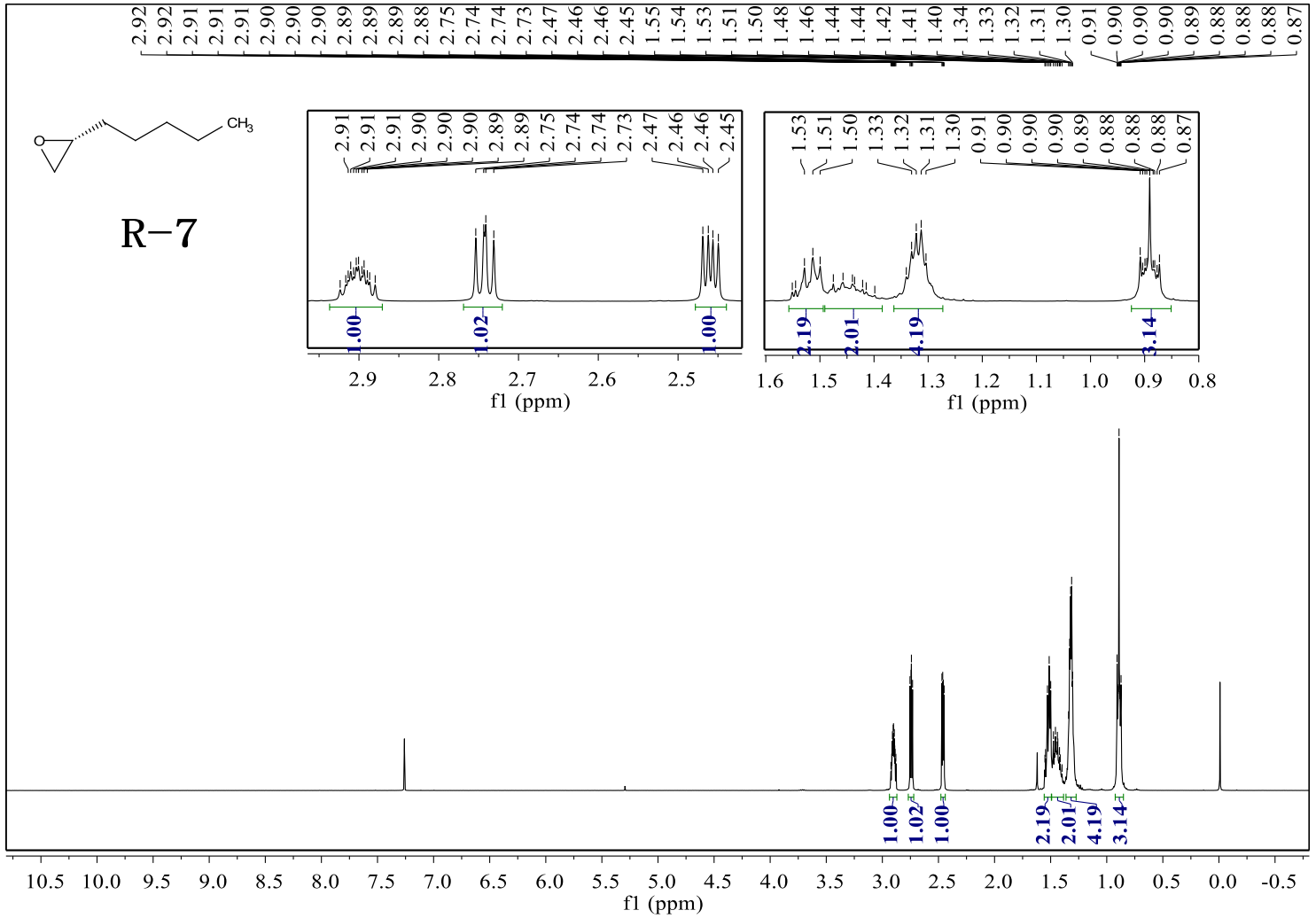
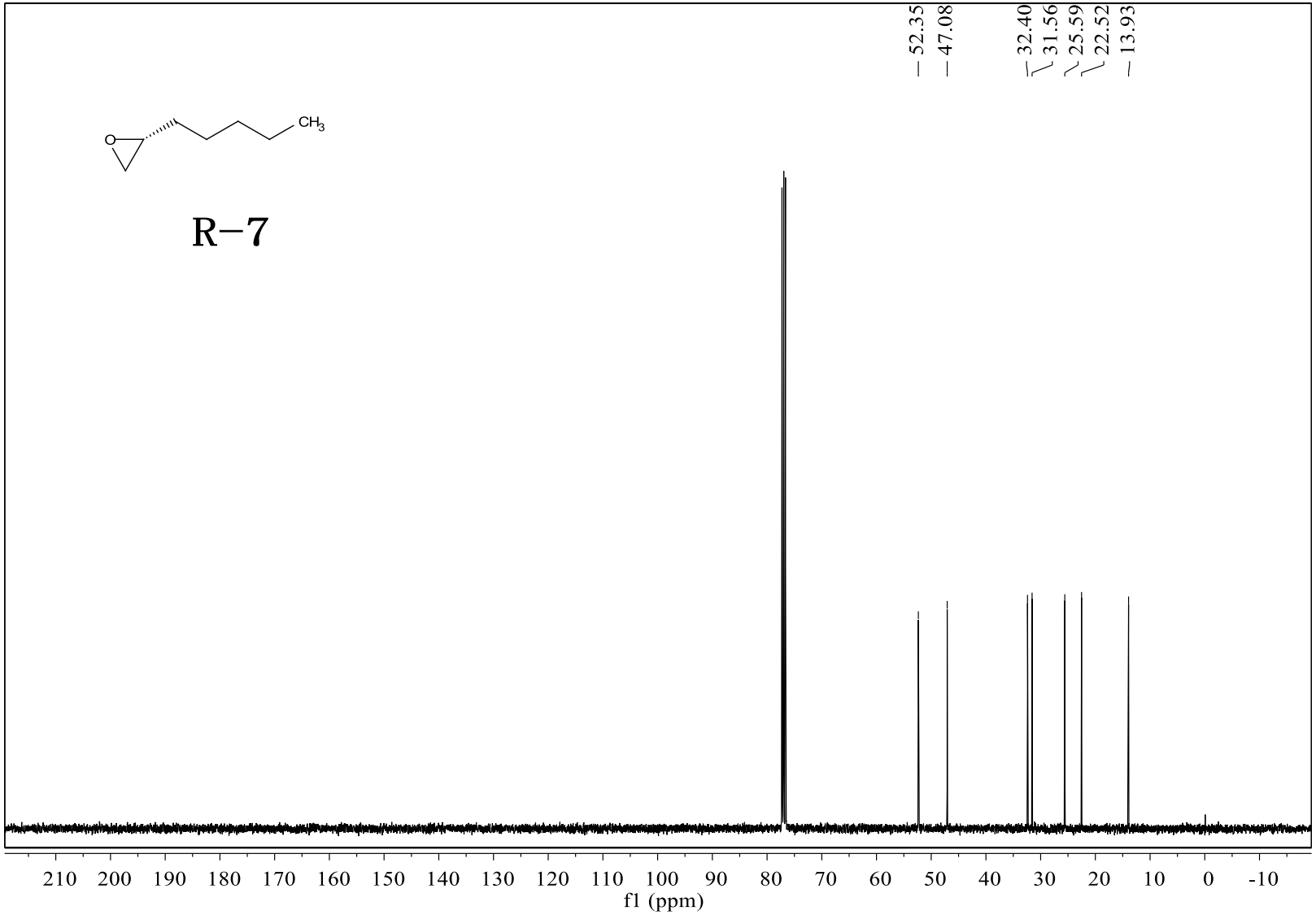
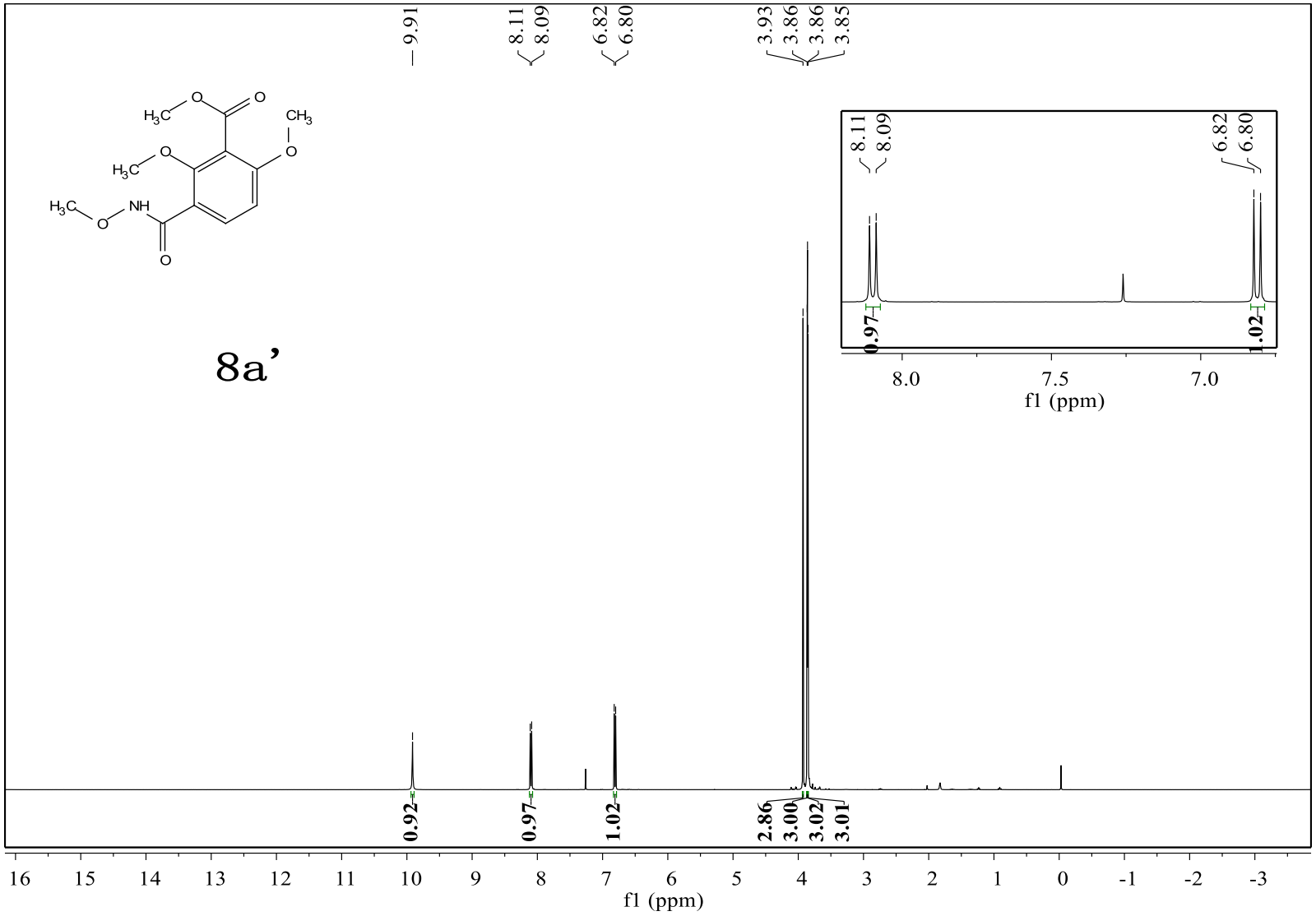


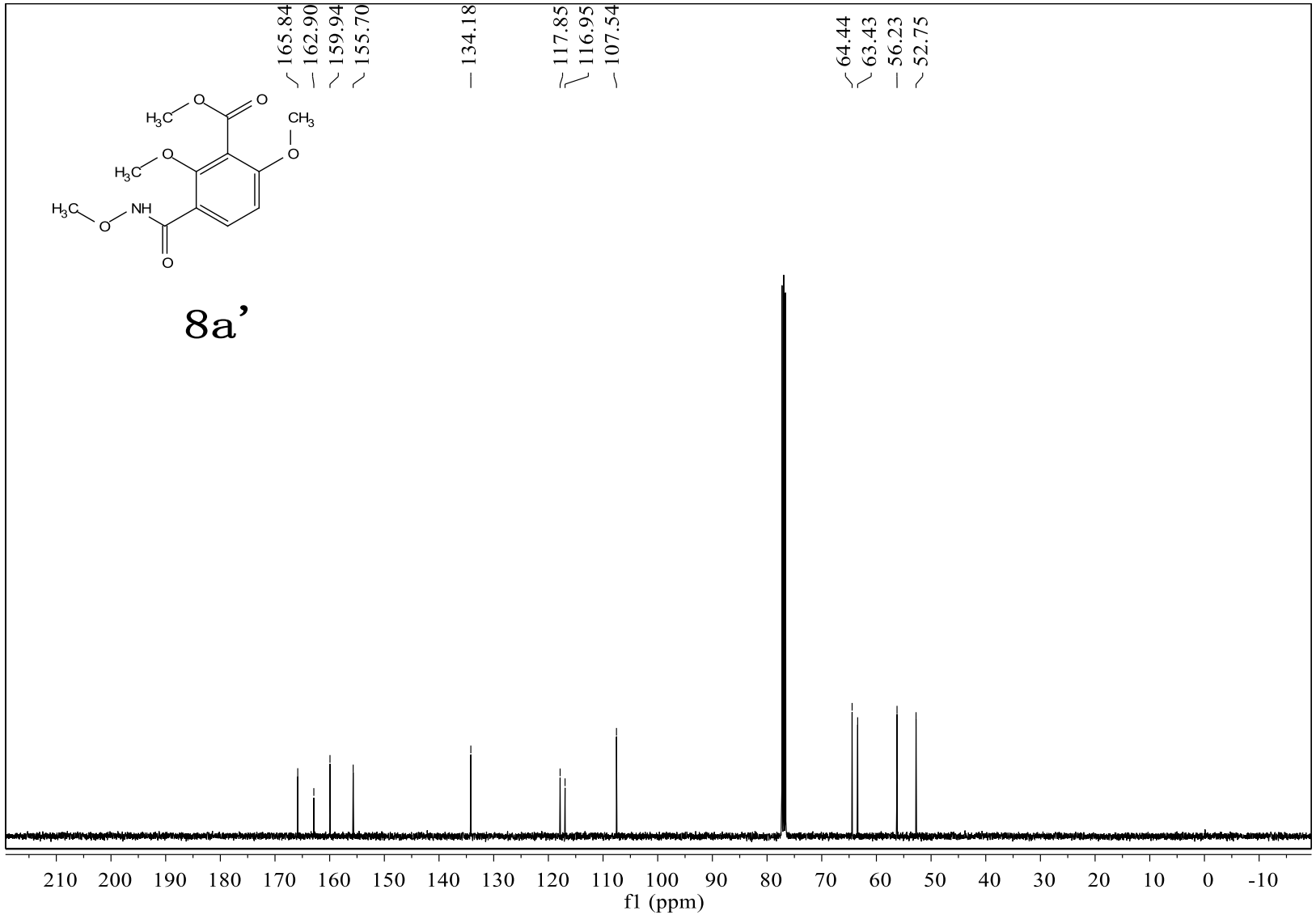
Figure 1. Effect of selected compounds on cell viability. Data represent percent viability as mean ± SD of three replicates per concentration of each compound.

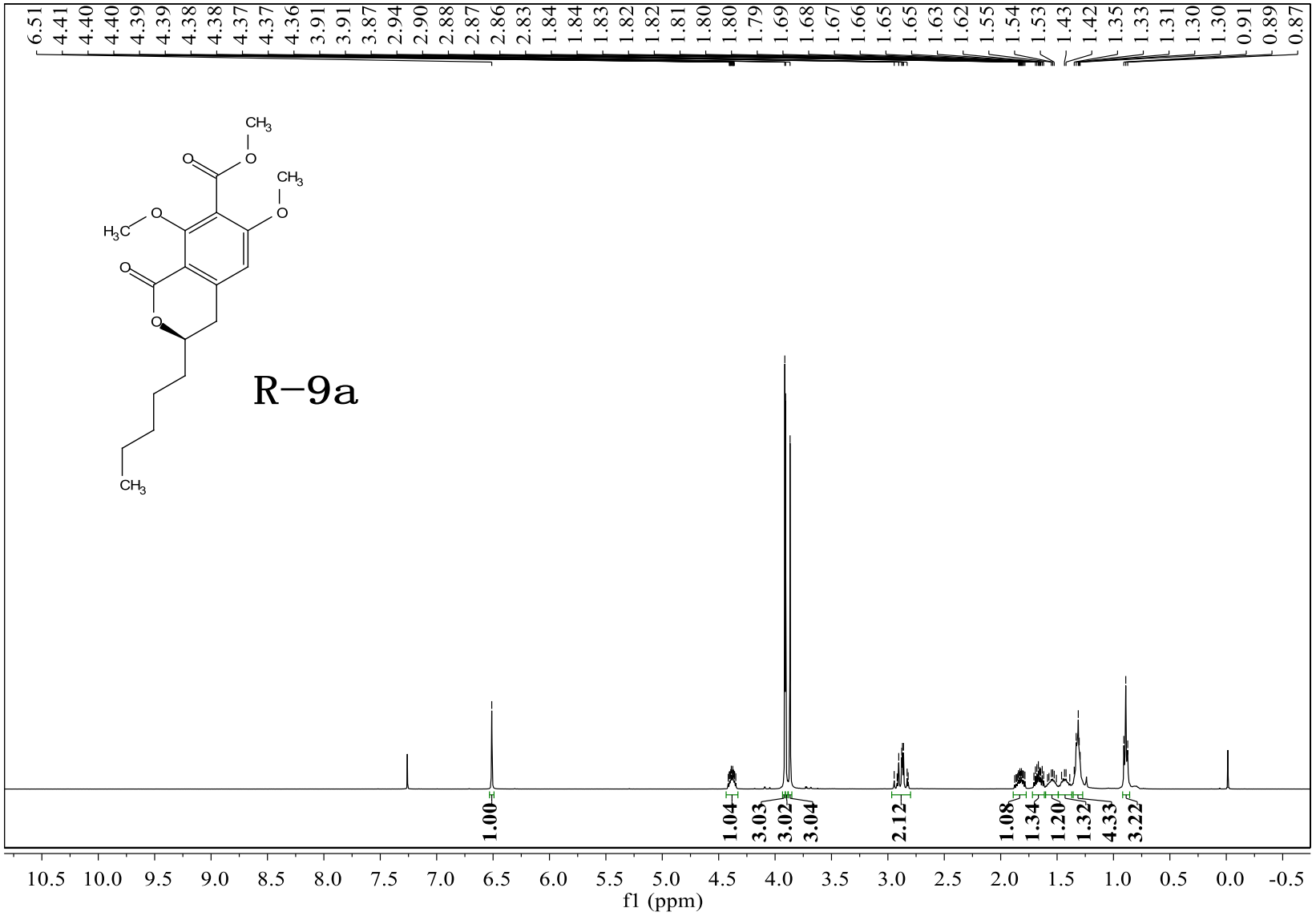
6. Copies of ^{1}H, ^{13}C NMR Spectra

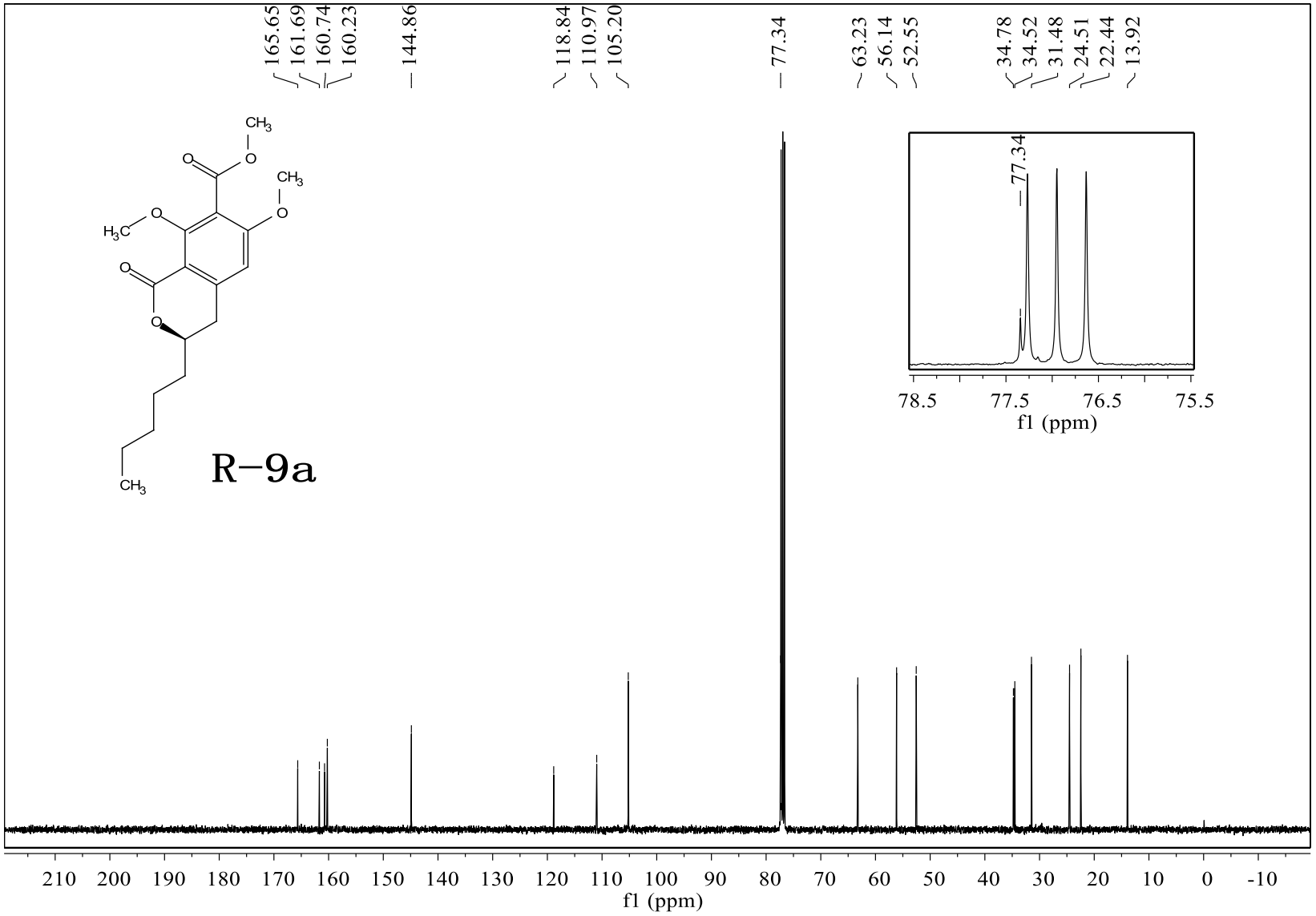


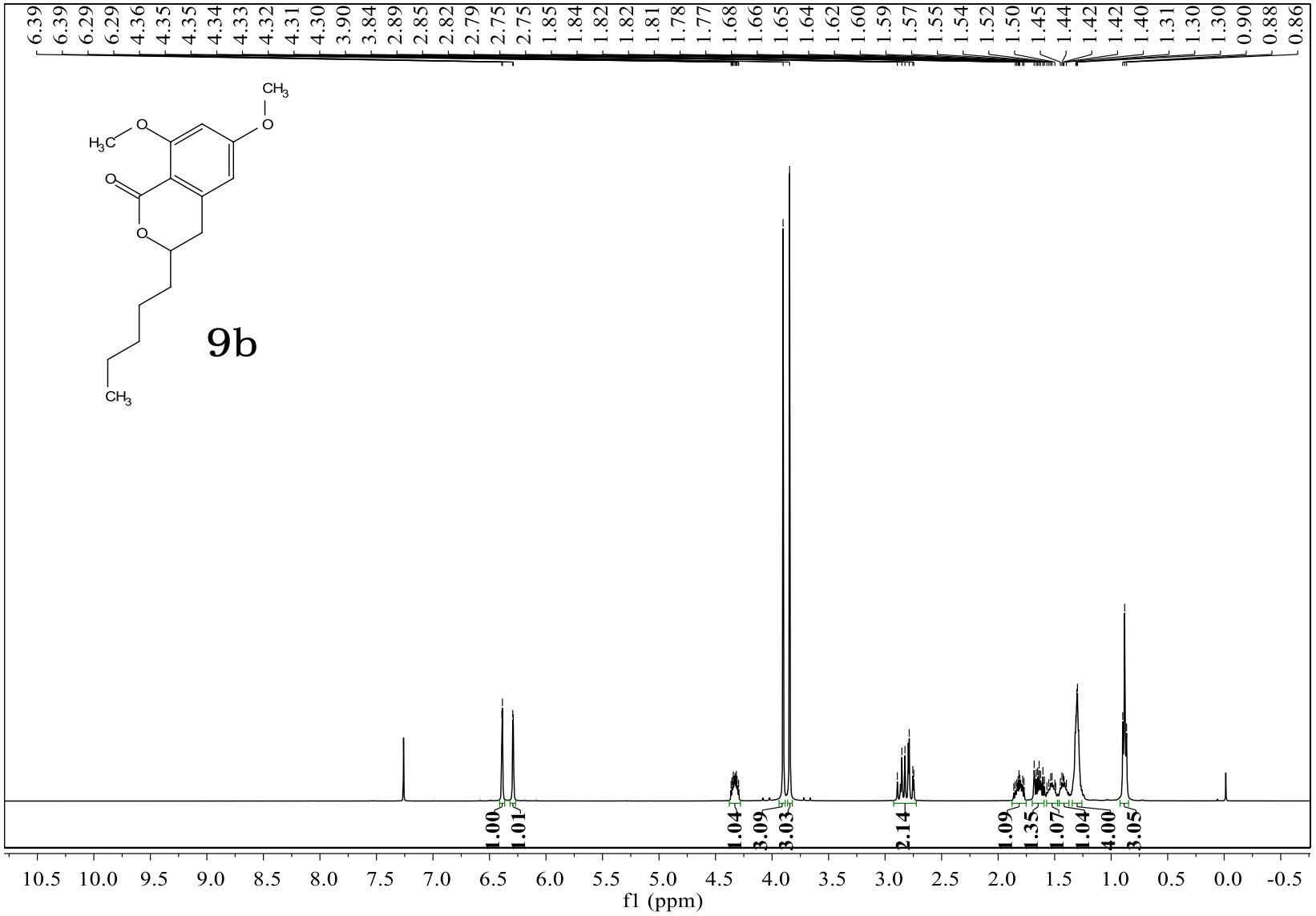

52.35
47.08
32.40
31.56
25.59
22.52
13.93
CH3
R−7
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

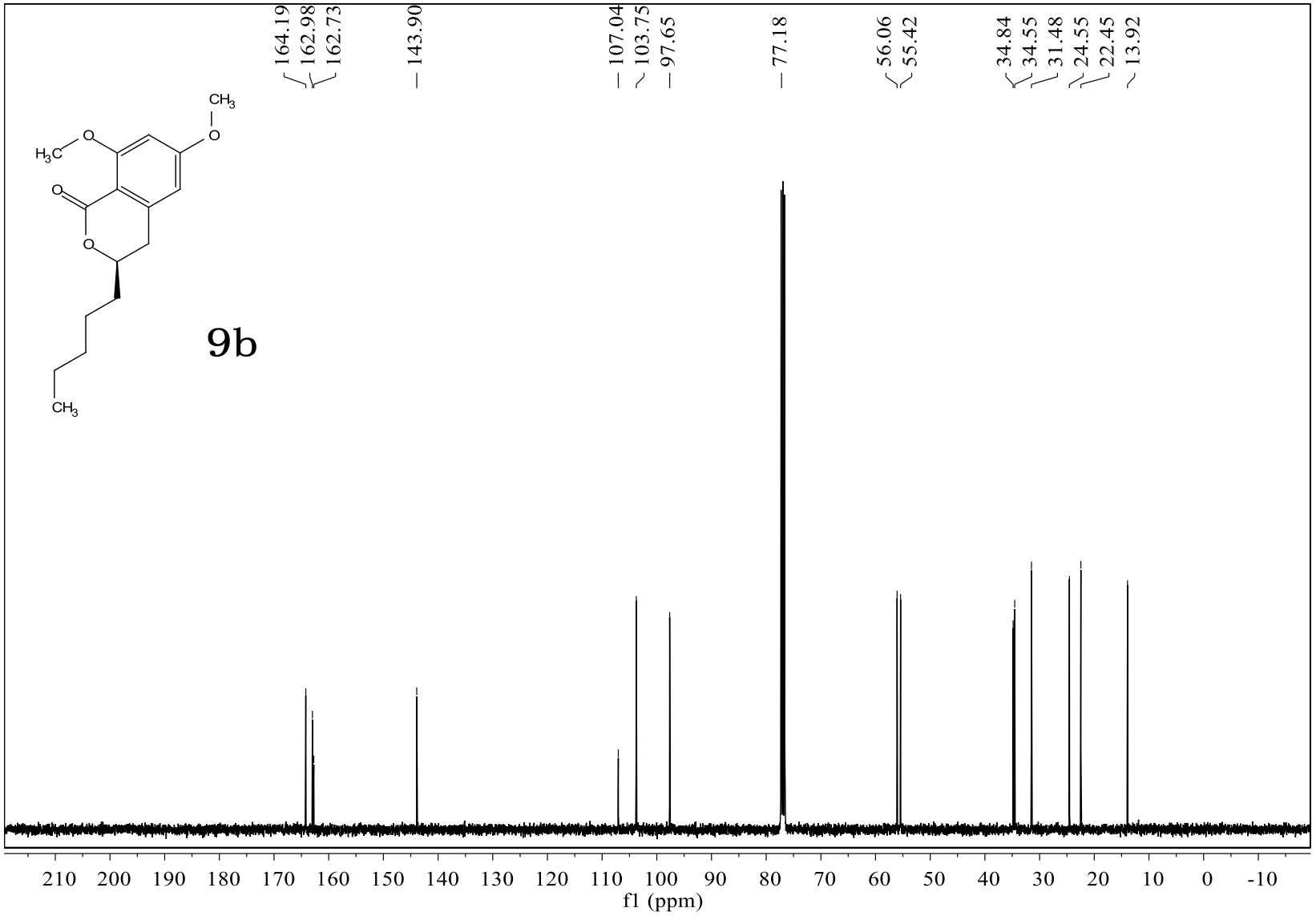

9.91
8.11
8.09
6.82
6.80
3.93
3.86
3.86
3.85
8a'
0.92
0.97
1.02
2.86
3.00
3.02
3.01
f1 (ppm)
0.97
1.02
8.0
7.5
7.0
f1 (ppm)


165.84
162.90
159.94
155.70
134.18
117.85
116.95
107.54
64.44
63.43
56.23
52.75
8a'
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


6.51 4.41 4.40 4.40 4.39 4.39 4.38 4.38 4.37 4.37 4.36 3.91 3.91 3.87 2.94 2.90 2.88 2.87 2.86 2.83 1.84 1.84 1.83 1.82 1.82 1.81 1.80 1.80 1.79 1.69 1.68 1.67 1.66 1.65 1.65 1.63 1.62 1.55 1.54 1.53 1.43 1.42 1.35 1.33 1.31 1.30 1.30 0.91 0.89 0.87
R−9a
1.00 1.04 3.03 3.02 3.04 2.12 1.08 1.34 1.20 1.32 4.33 3.22
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


165.65
161.69
160.74
160.23
144.86
118.84
110.97
105.20
77.34
63.23
56.14
52.55
34.78
34.52
31.48
24.51
22.44
13.92
R−9a
77.34
78.5
77.5
76.5
75.5
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


6.39 6.39 6.29 6.29 4.36 4.35 4.35 4.34 4.33 4.32 4.31 4.30 3.90 3.84 2.89 2.85 2.82 2.79 2.75 2.75 1.85 1.84 1.82 1.82 1.81 1.78 1.77 1.68 1.66 1.65 1.64 1.62 1.60 1.59 1.57 1.55 1.54 1.52 1.50 1.45 1.44 1.42 1.42 1.40 1.31 1.30 1.30 0.90 0.88 0.86
CH3
O
H3C
O
O
O
CH3
9b
1.00 1.01 1.04 3.09 3.03 2.14 1.09 1.35 1.07 1.04 4.00 3.05
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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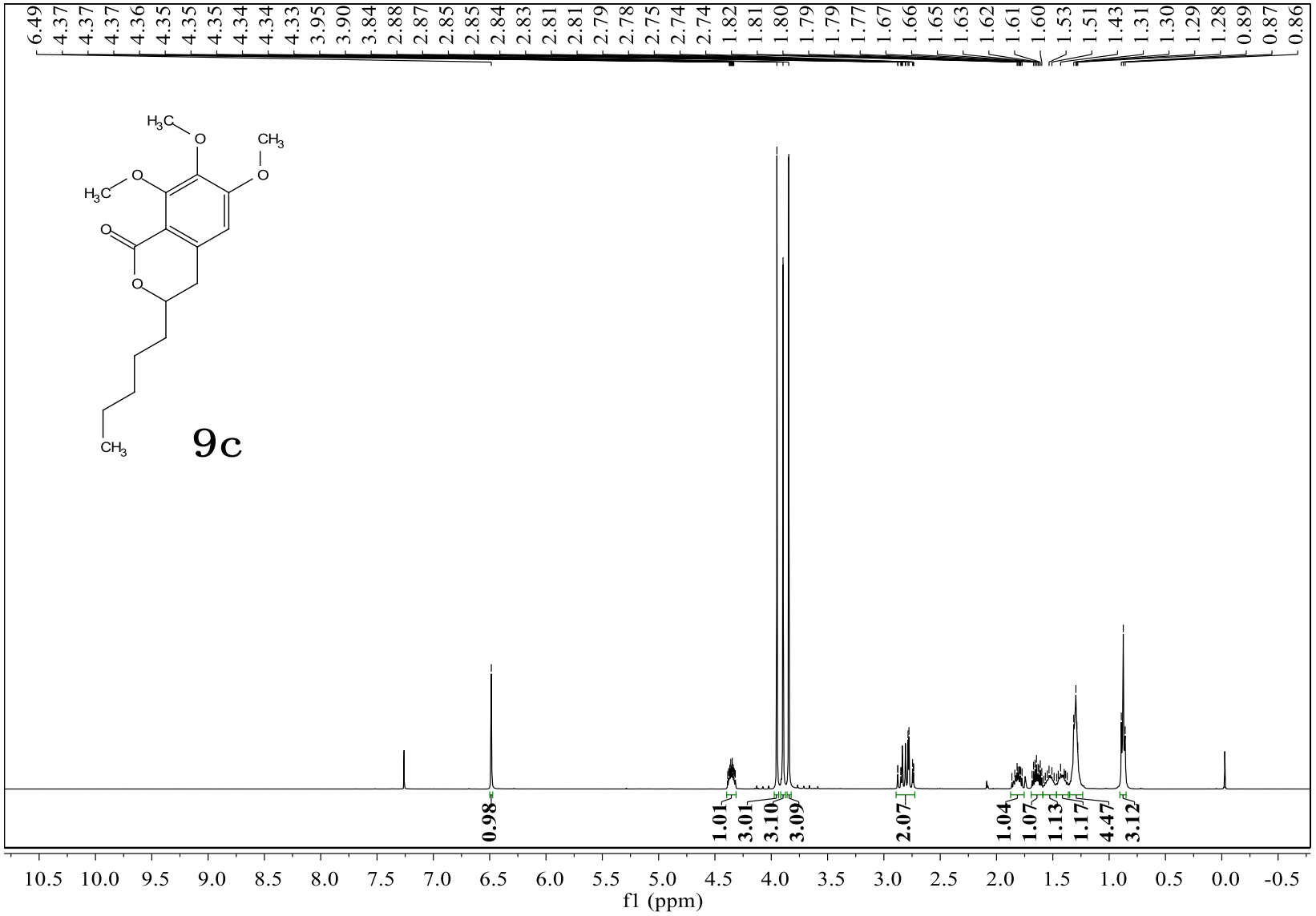
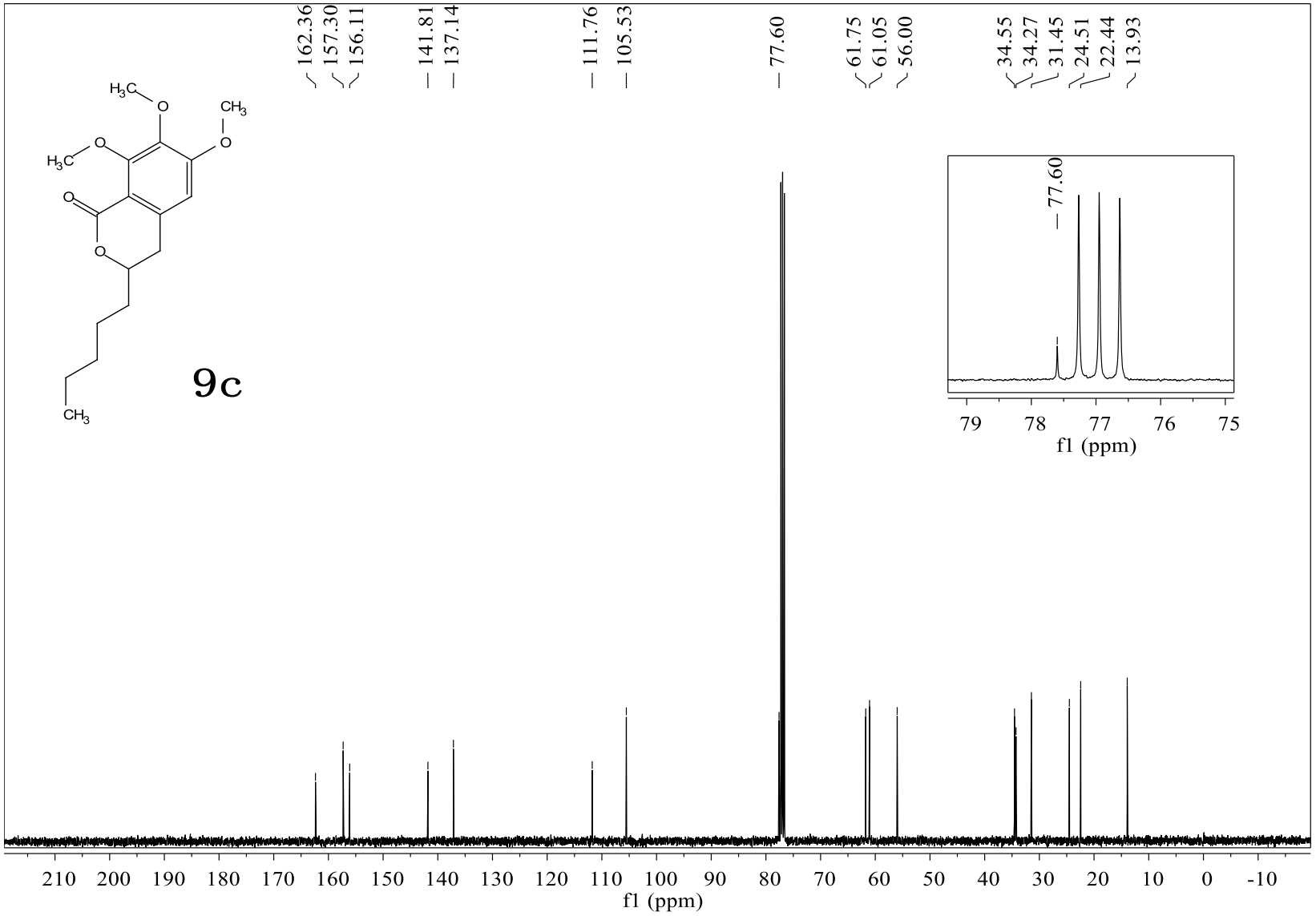
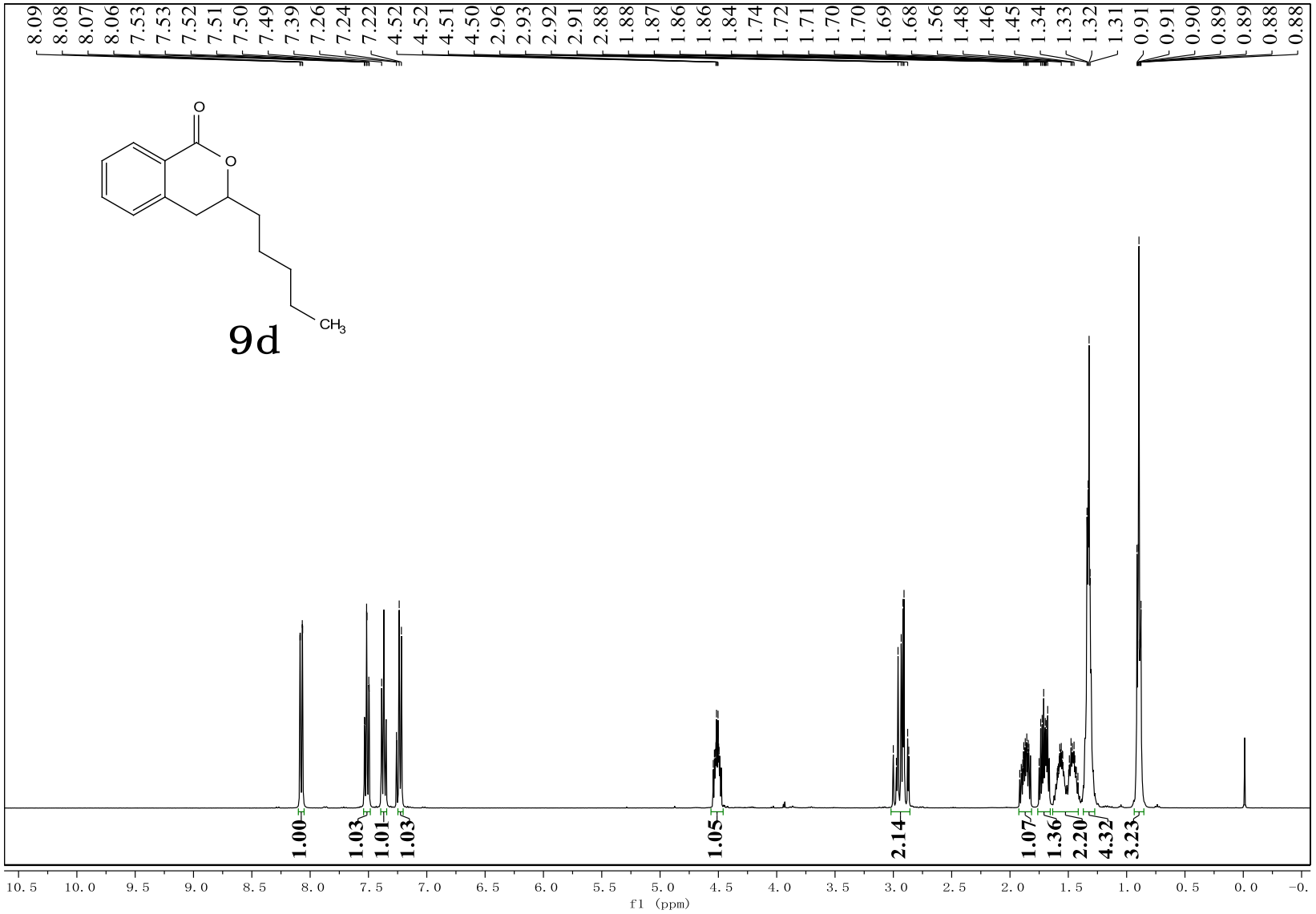
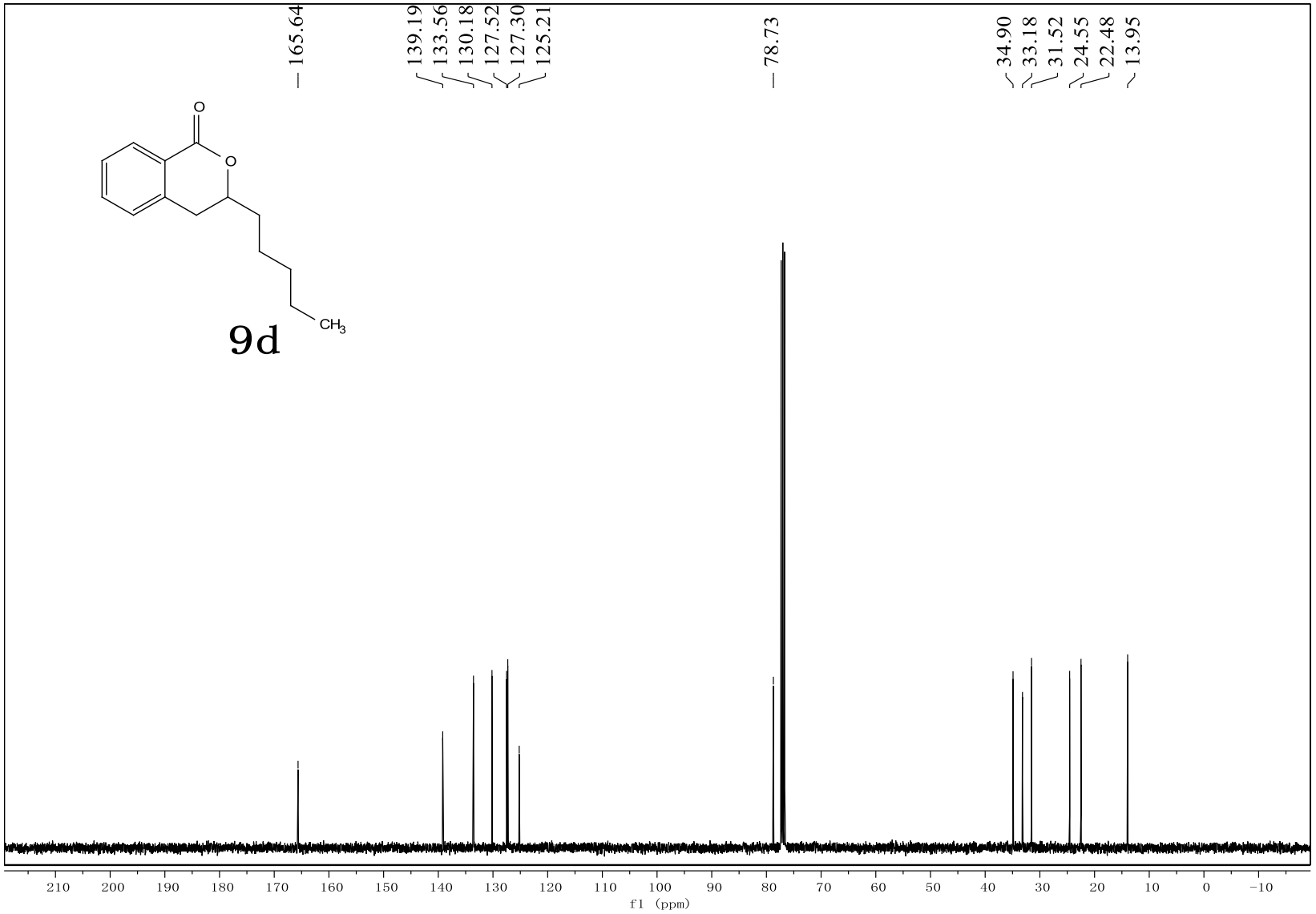
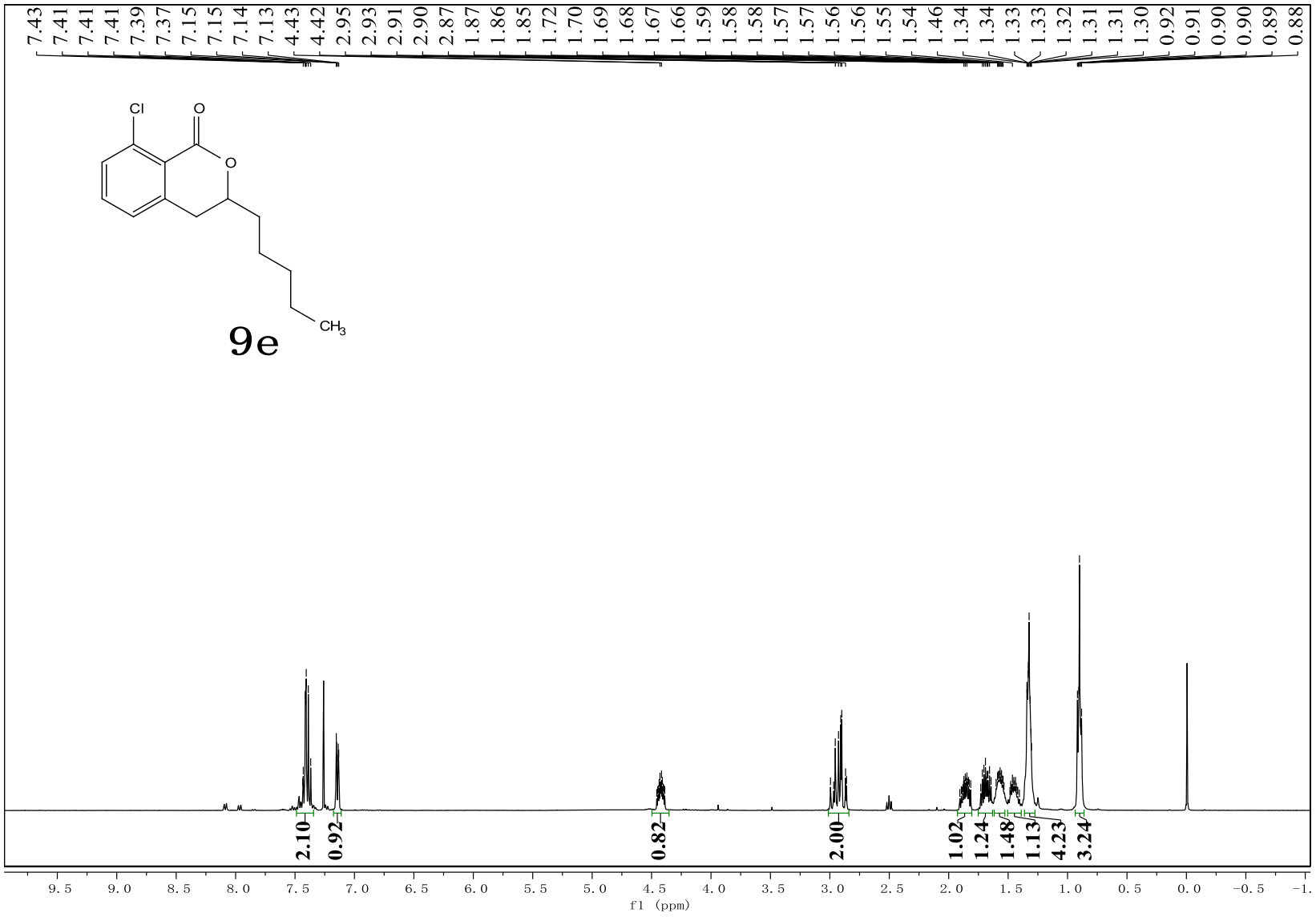
162.73
143.90
107.04
103.75
97.65
77.18
56.06
55.42
34.84
34.55
31.48
24.55
22.45
13.92
9b
CH3
O
H3C
O
O
O
CH3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

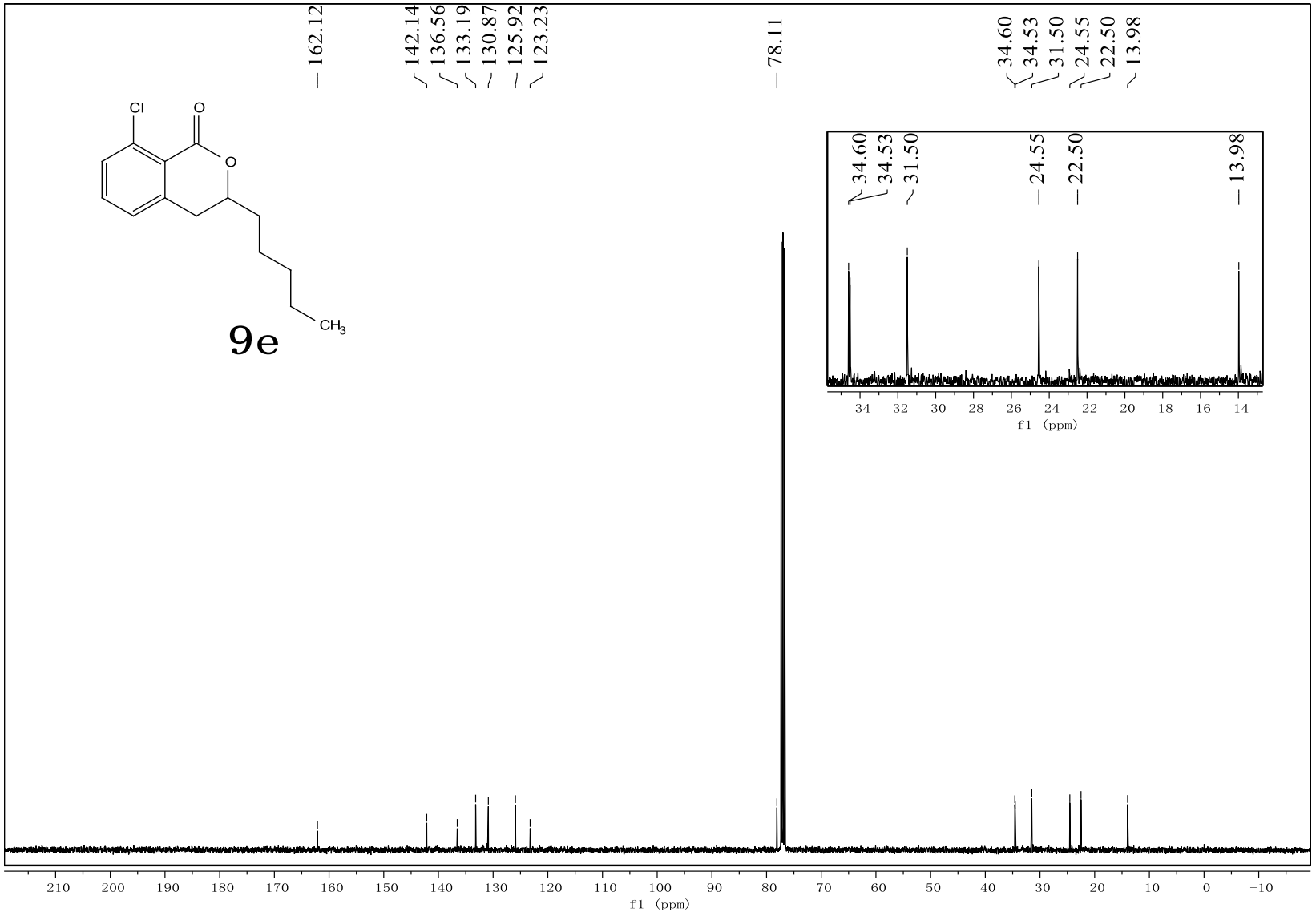

6.49 4.37 4.37 4.37 4.36 4.35 4.35 4.35 4.34 4.34 4.33 3.95 3.90 3.84 2.88 2.87 2.85 2.85 2.84 2.83 2.81 2.81 2.79 2.78 2.75 2.74 2.74 1.82 1.81 1.80 1.79 1.79 1.77 1.67 1.66 1.65 1.63 1.62 1.61 1.60 1.53 1.51 1.43 1.31 1.30 1.29 1.28 0.89 0.87 0.86
H3C
O
CH3
O
H3C
O
O
O
CH3
9c
0.98
1.01
3.01
3.10
3.09
2.07
1.04
1.07
1.13
1.17
4.47
3.12
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


162.36
157.30
156.11
141.81
137.14
111.76
105.53
77.60
61.75
61.05
56.00
34.55
34.27
31.45
24.51
22.44
13.93
9c
77.60
79 78 77 76 75
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


8.09 8.08 8.07 8.06 7.53 7.53 7.52 7.51 7.50 7.49 7.39 7.26 7.24 7.22 4.52 4.52 4.51 4.50 2.96 2.93 2.92 2.91 2.88 1.88 1.87 1.86 1.86 1.84 1.74 1.72 1.71 1.70 1.70 1.69 1.68 1.56 1.48 1.46 1.45 1.34 1.33 1.32 1.31 0.91 0.91 0.90 0.89 0.89 0.88 0.88
O
O
CH3
9d
1.00
1.03
1.01
1.03
1.05
2.14
1.07
1.36
2.20
4.32
3.23
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.
f1 (ppm)


165.64
139.19
133.56
130.18
127.52
127.30
125.21
78.73
34.90
33.18
31.52
24.55
22.48
13.95
O
O
CH3
9d
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)


7.43
7.41
7.41
7.41
7.39
7.37
7.15
7.15
7.14
7.13
4.43
4.42
2.95
2.93
2.91
2.90
2.87
1.87
1.86
1.85
1.72
1.70
1.69
1.68
1.67
1.66
1.59
1.58
1.58
1.57
1.57
1.56
1.56
1.55
1.54
1.46
1.34
1.34
1.33
1.33
1.32
1.31
1.31
1.30
0.92
0.91
0.90
0.90
0.89
0.88
Cl
O
O
CH3
9e
2.10
0.92
0.82
2.00
1.02
1.24
1.48
1.13
4.23
3.24
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
−0.5
−1.
f1 (ppm)


162.12
142.14
136.56
133.19
130.87
125.92
123.23
78.11
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34.53
31.50
24.55
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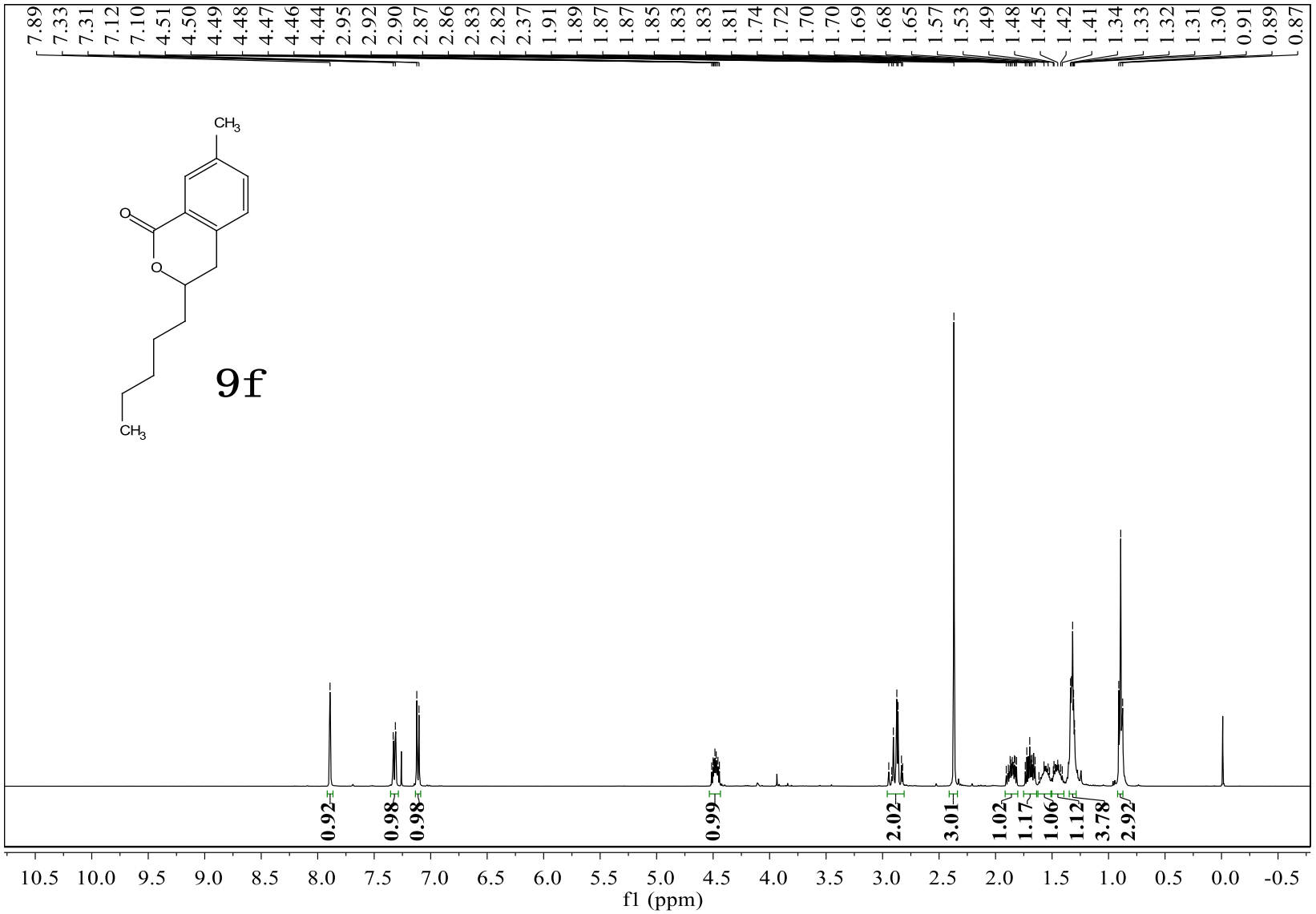
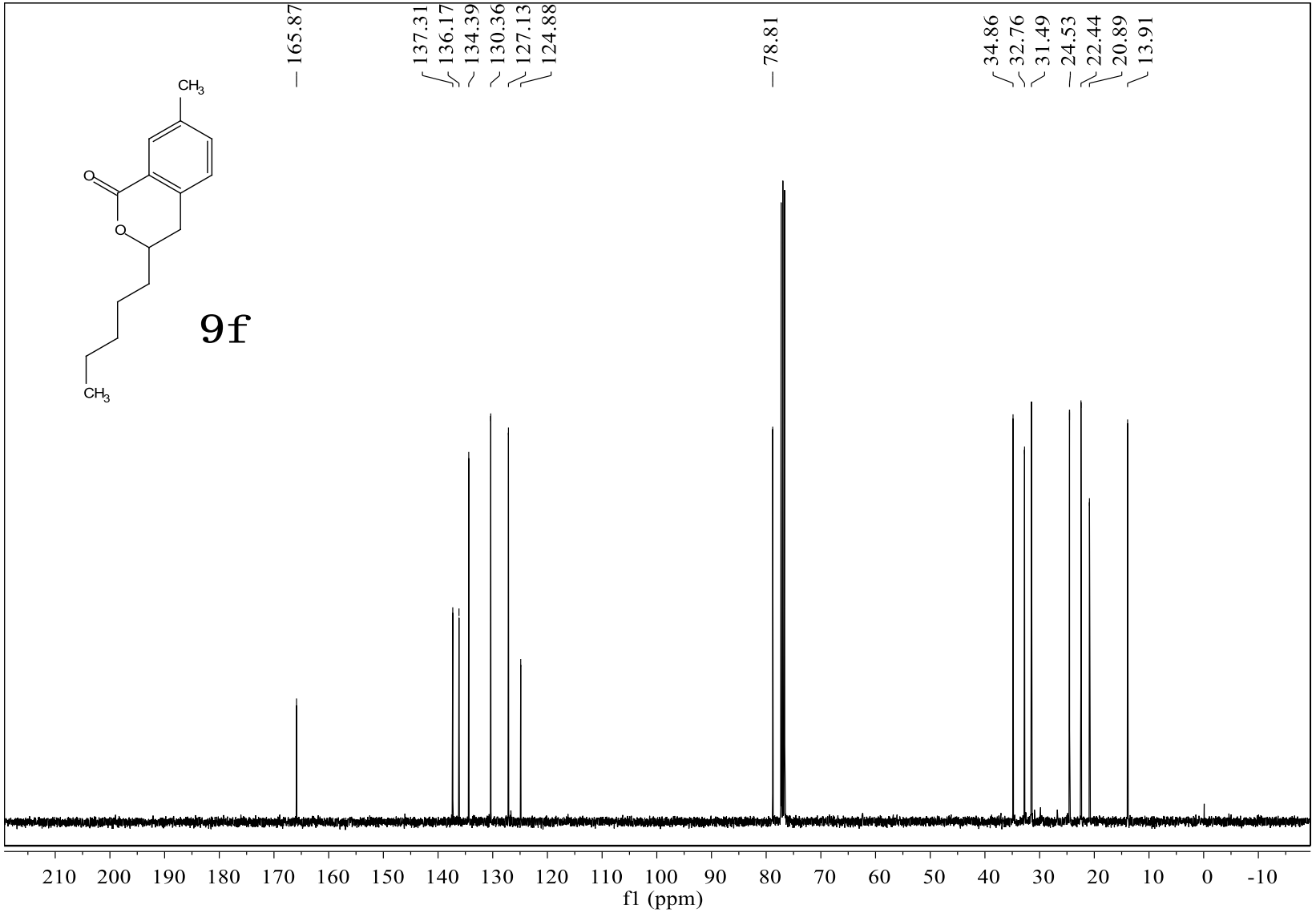
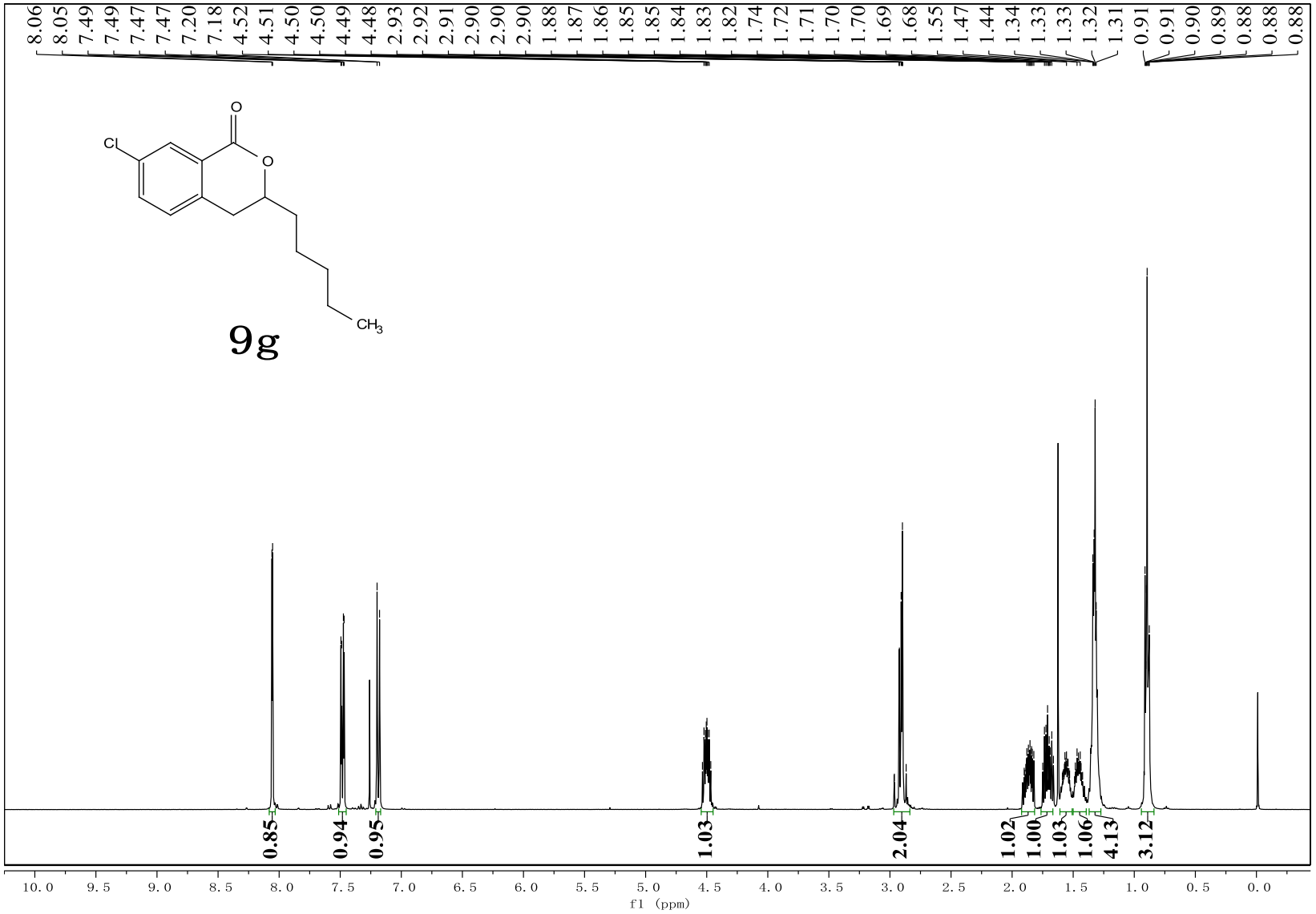
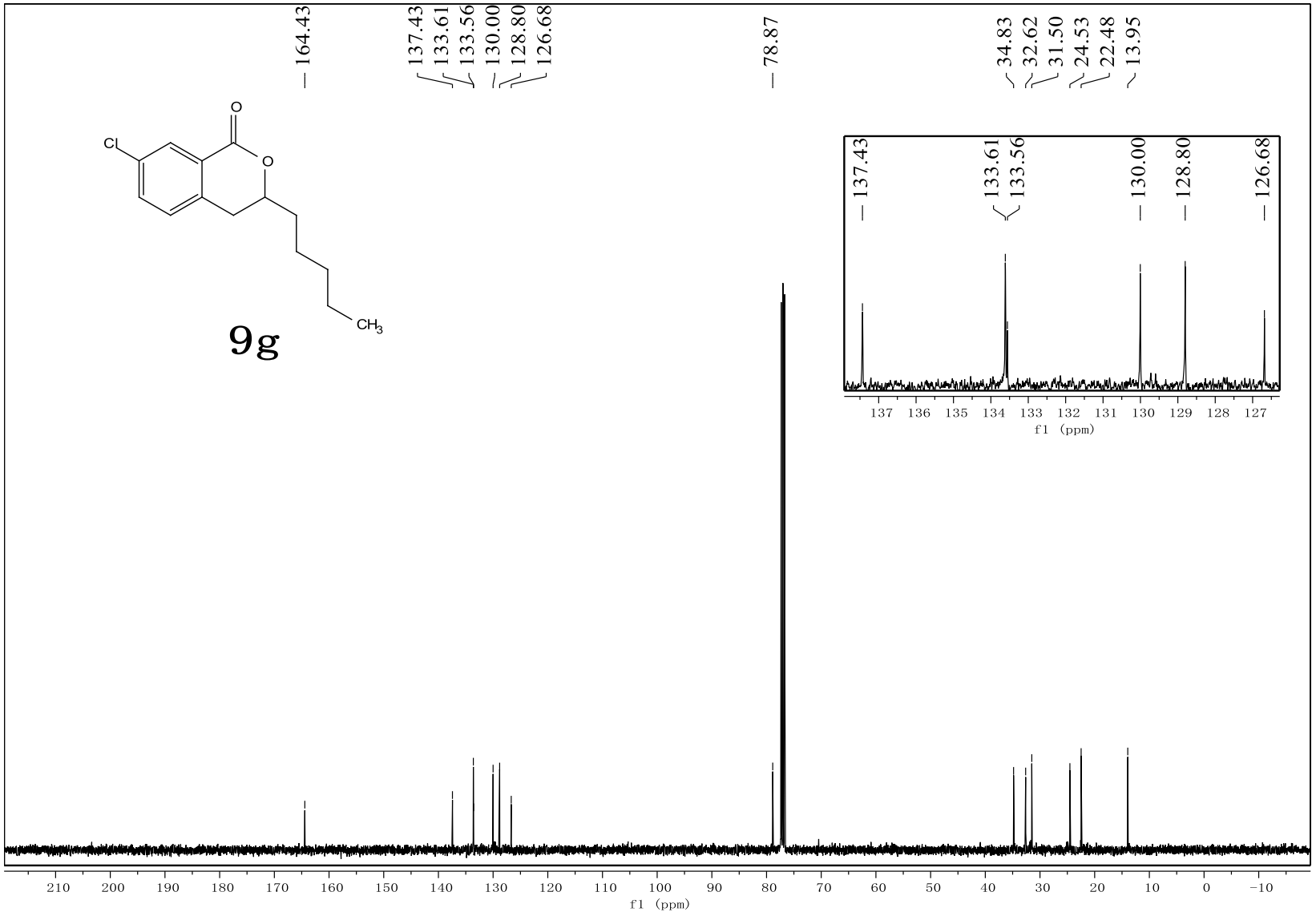
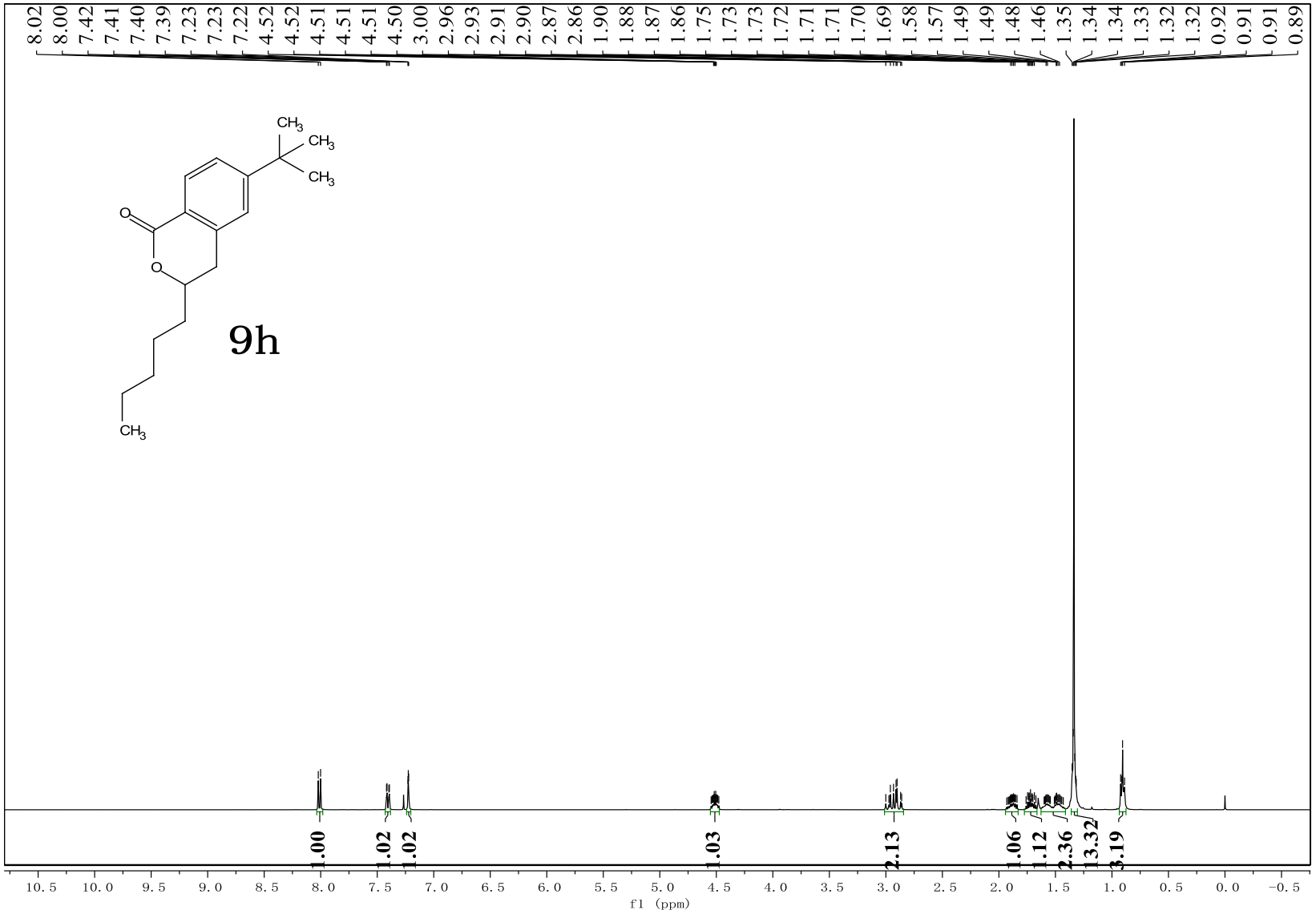
Cl
O
O
CH3
9e
f1 (ppm)

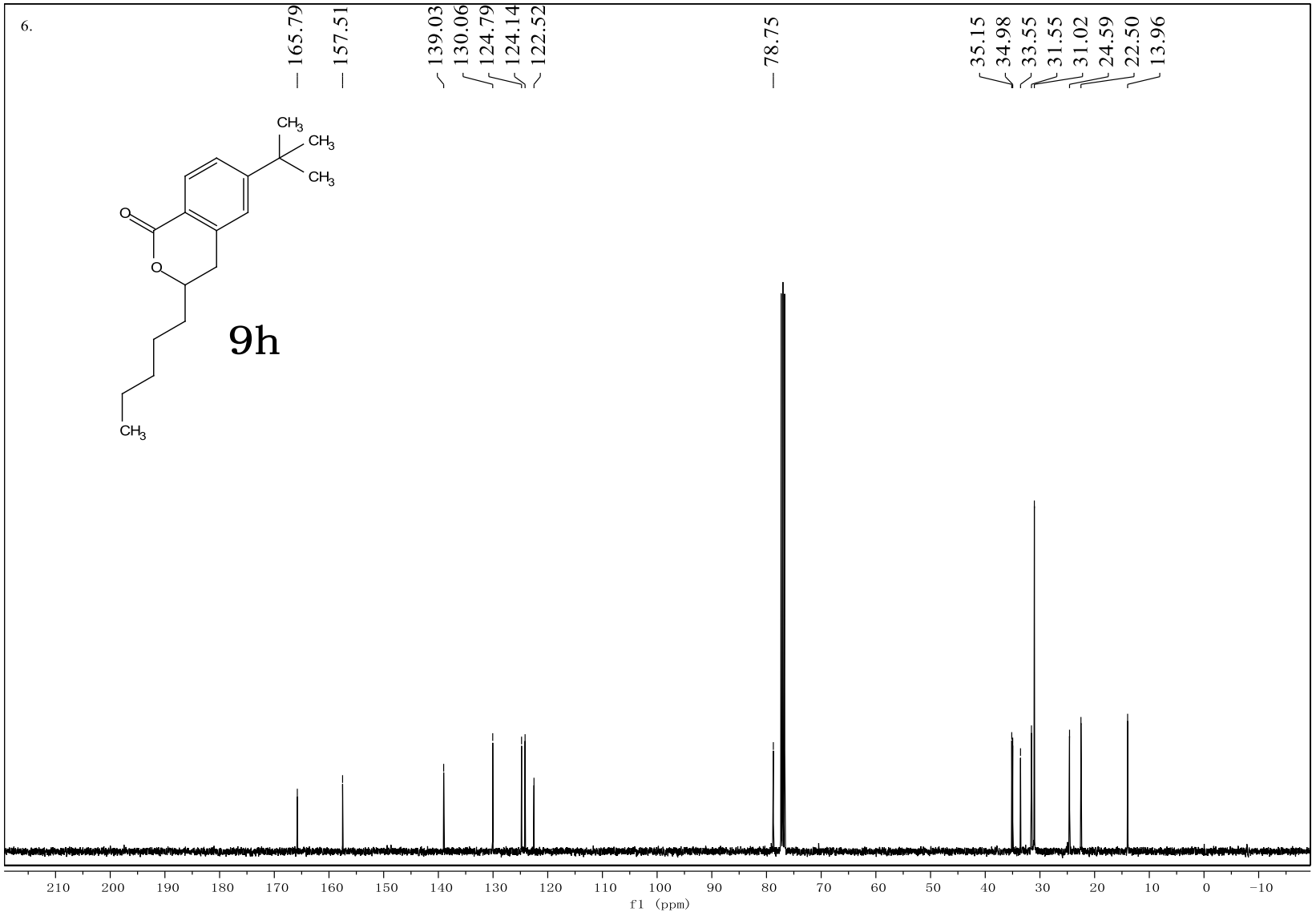

7.89 7.33 7.31 7.12 7.10 4.51 4.50 4.49 4.48 4.47 4.46 4.44 2.95 2.92 2.90 2.87 2.86 2.83 2.82 2.37 1.91 1.89 1.87 1.87 1.85 1.83 1.83 1.81 1.74 1.72 1.70 1.70 1.69 1.68 1.65 1.57 1.53 1.49 1.48 1.45 1.42 1.41 1.34 1.33 1.32 1.31 1.30 0.91 0.89 0.87
CH3
O
O
CH3
9f
0.92
0.98
0.98
0.99
2.02
3.01
1.02
1.17
1.06
1.12
3.78
2.92
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

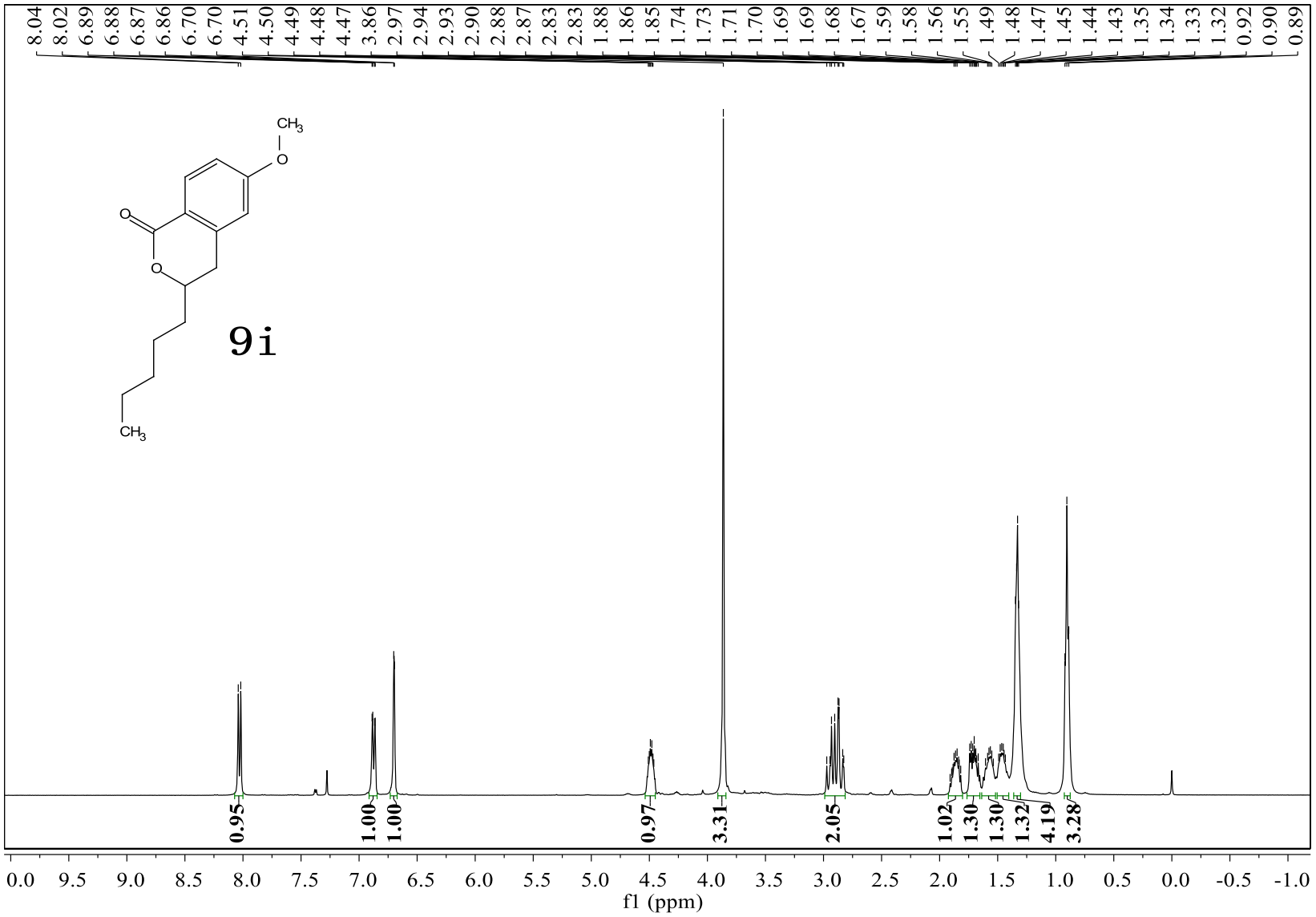

165.87
137.31
136.17
134.39
130.36
127.13
124.88
78.81
34.86
32.76
31.49
24.53
22.44
20.89
13.91
CH3
O
O
CH3
9f
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

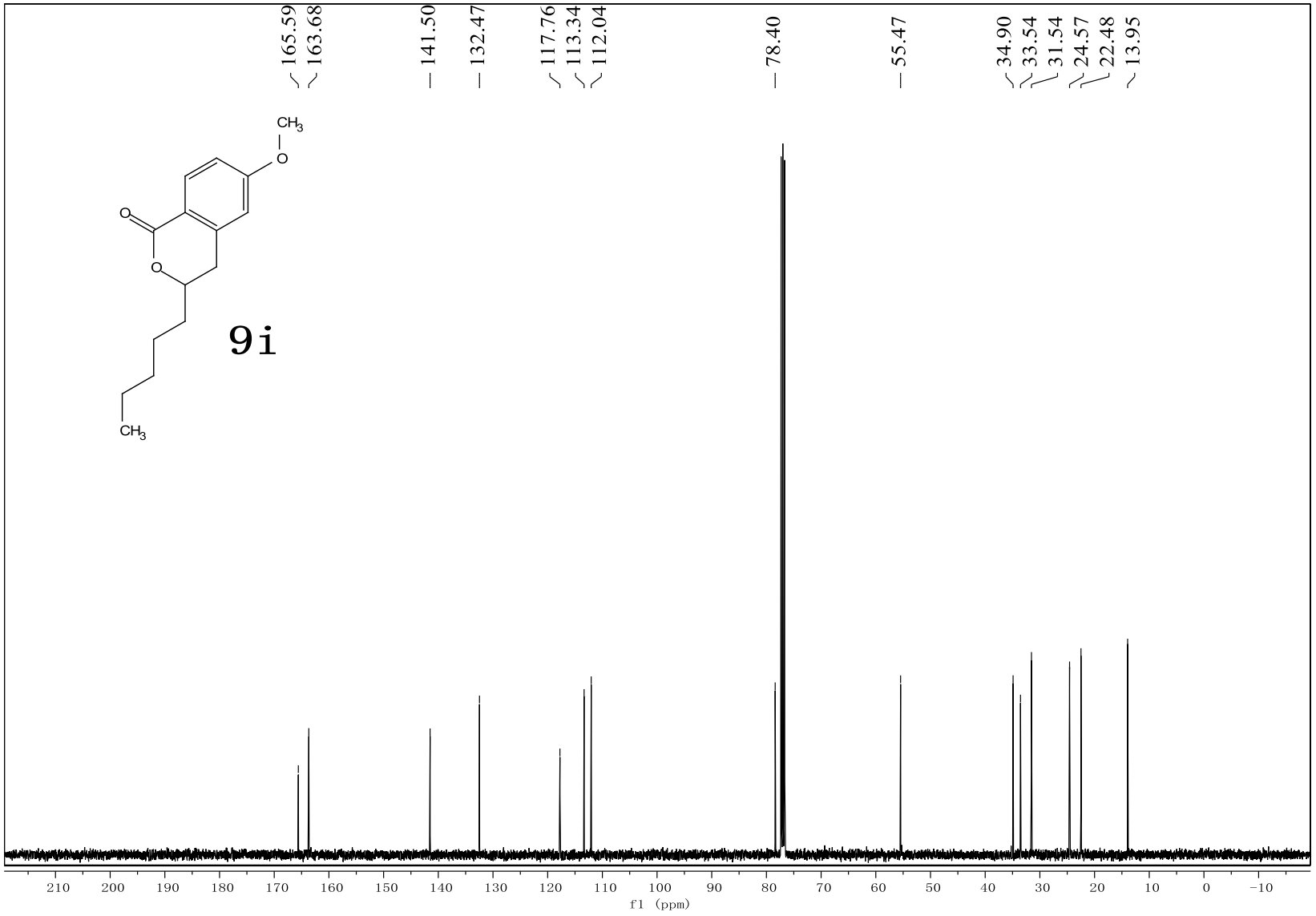

8.06 8.05 7.49 7.49 7.47 7.47 7.20 7.18 4.52 4.51 4.50 4.50 4.49 4.48 2.93 2.92 2.91 2.90 2.90 2.90 1.88 1.87 1.86 1.85 1.85 1.84 1.83 1.82 1.74 1.72 1.71 1.70 1.70 1.69 1.68 1.55 1.47 1.44 1.34 1.33 1.33 1.32 1.31 0.91 0.91 0.90 0.89 0.88 0.88 0.88
O
Cl
O
CH3
9g
0.85 0.94 0.95 1.03 2.04 1.02 1.00 1.03 1.06 4.13 3.12
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

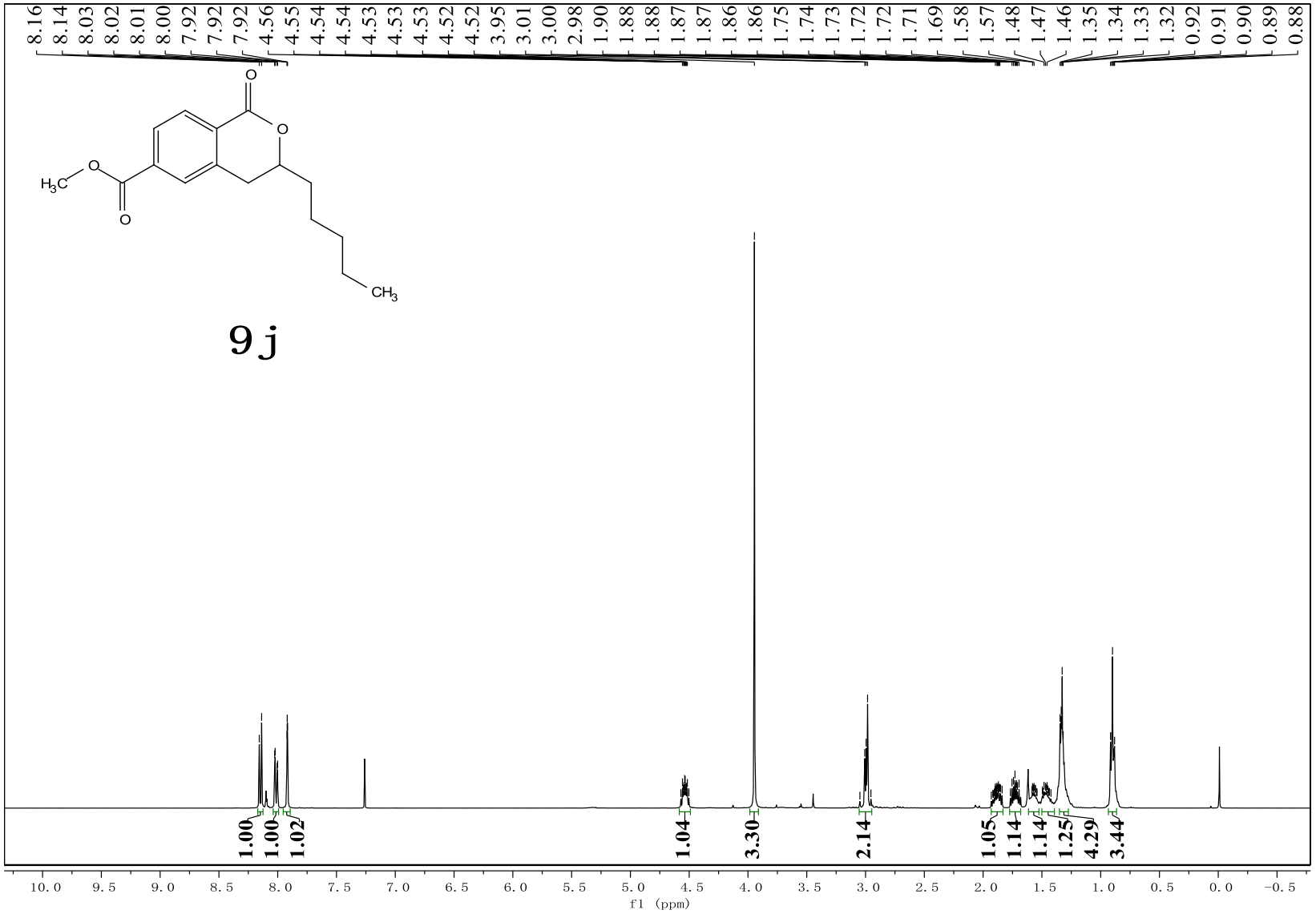

164.43
137.43
133.61
133.56
130.00
128.80
126.68
78.87
34.83
32.62
31.50
24.53
22.48
13.95
Cl
O
O
CH3
9g
f1 (ppm)

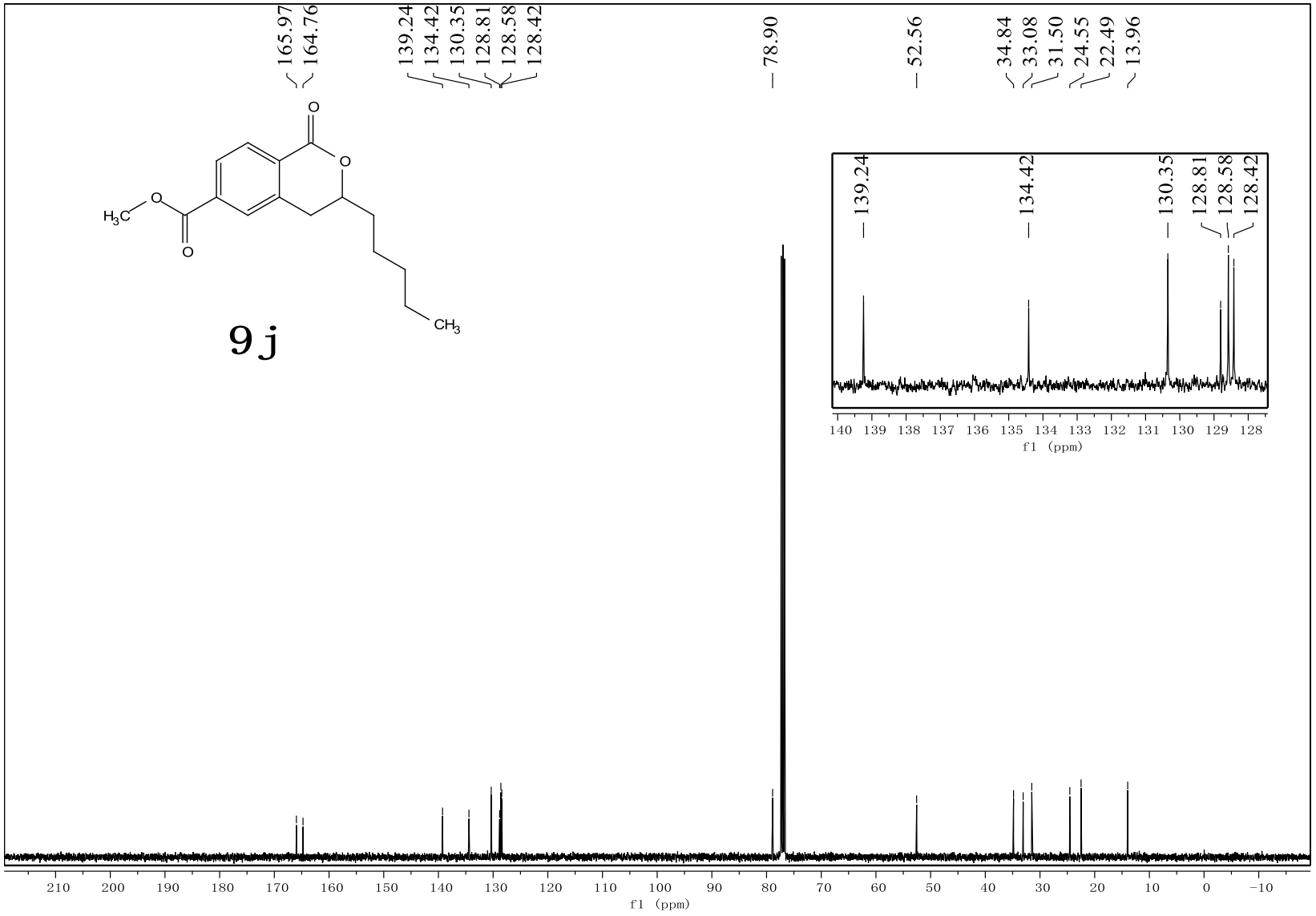

8.02 8.00 7.42 7.41 7.40 7.39 7.23 7.23 7.22 4.52 4.52 4.51 4.51 4.51 4.50 3.00 2.96 2.93 2.91 2.90 2.87 2.86 1.90 1.88 1.87 1.86 1.75 1.73 1.73 1.72 1.71 1.71 1.70 1.69 1.58 1.57 1.49 1.49 1.48 1.46 1.35 1.34 1.34 1.33 1.32 1.32 0.92 0.91 0.91 0.89
CH3
CH3
CH3
O
O
CH3
9h
1.00
1.02
1.02
1.03
2.13
1.06
1.12
2.36
13.32
3.19
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

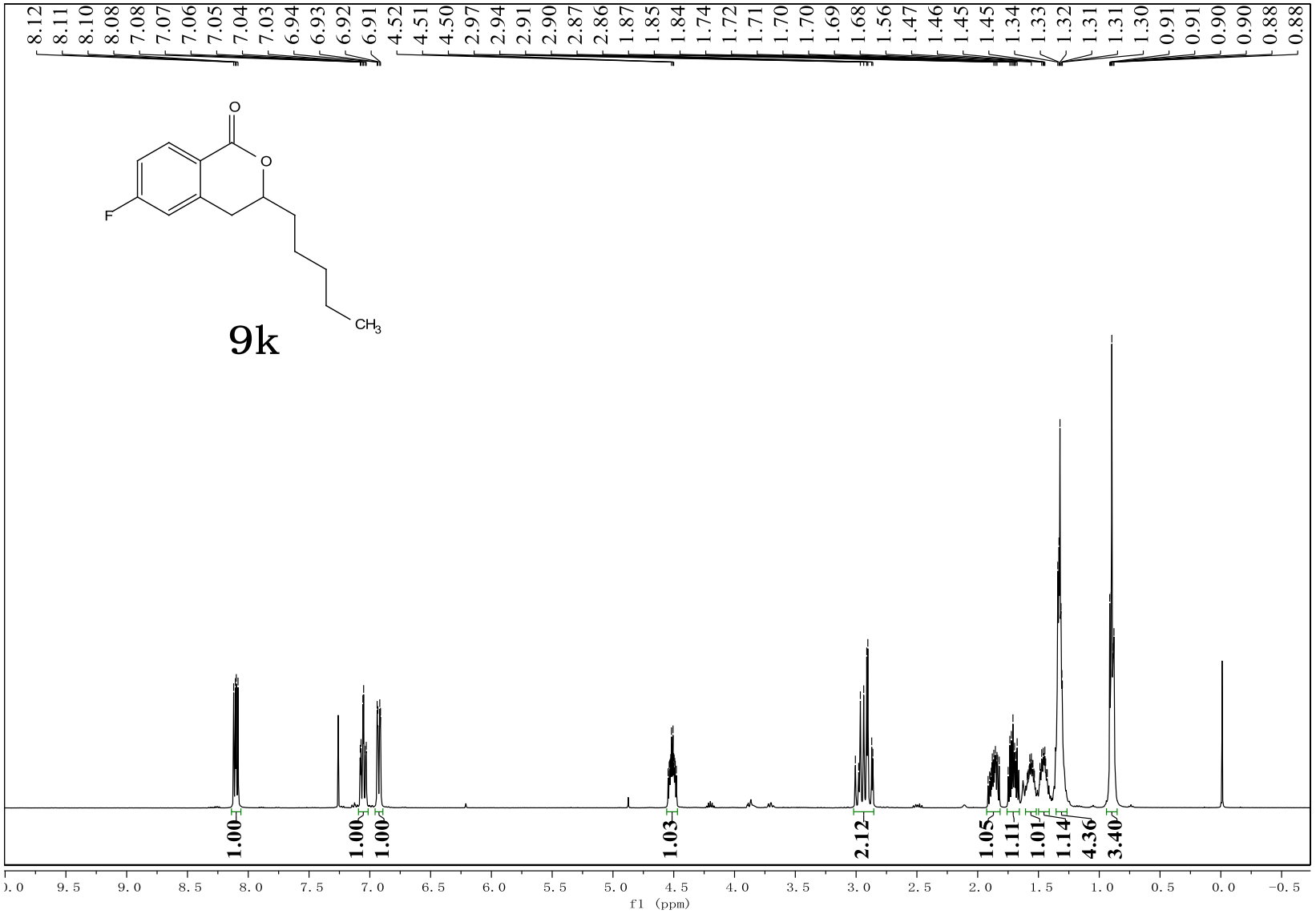

6.
165.79
157.51
139.03
130.06
124.79
124.14
122.52
78.75
35.15
34.98
33.55
31.55
31.02
24.59
22.50
13.96
CH3
CH3
CH3
O
O
CH3
9h
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)

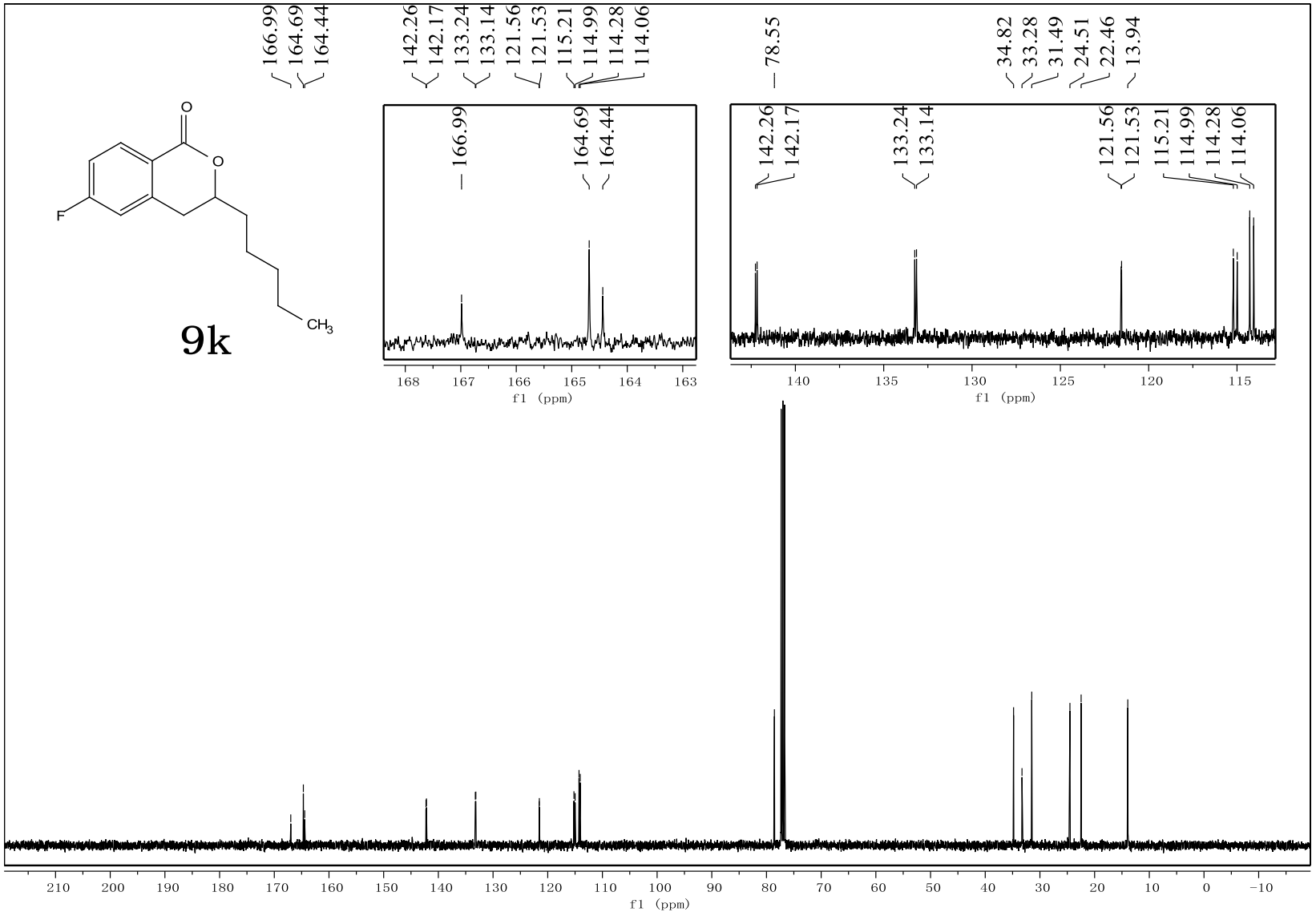

8.04 8.02 6.89 6.88 6.87 6.86 6.70 6.70 4.51 4.50 4.49 4.48 4.47 3.86 2.97 2.94 2.93 2.90 2.88 2.87 2.83 2.83 1.88 1.86 1.85 1.74 1.73 1.71 1.70 1.69 1.69 1.68 1.67 1.59 1.58 1.56 1.55 1.49 1.48 1.47 1.45 1.44 1.43 1.35 1.34 1.33 1.32 0.92 0.90 0.89
CH3
O
O
O
CH3
9i
0.95
1.00
1.00
0.97
3.31
2.05
1.02
1.30
1.30
1.32
4.19
3.28
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

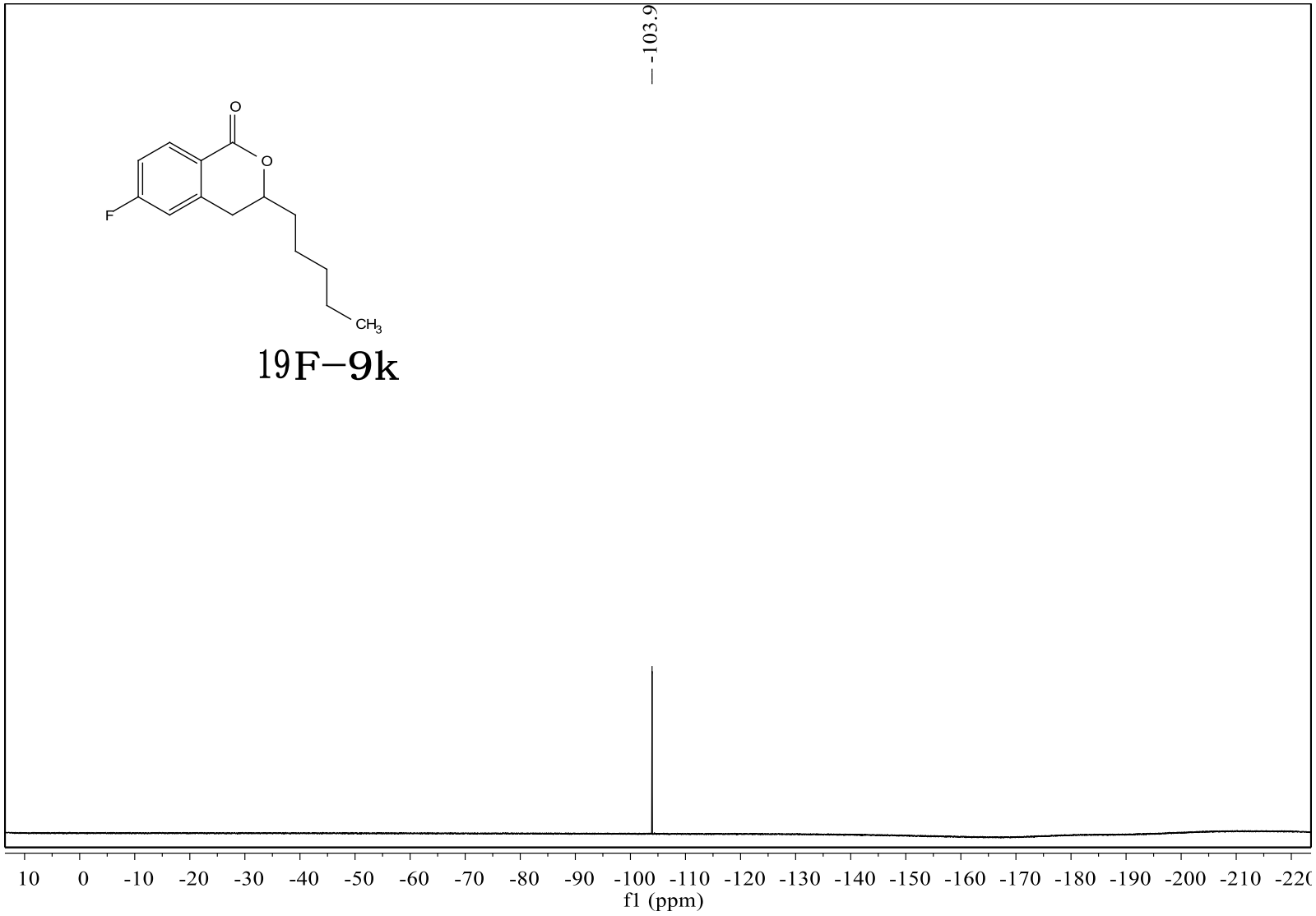

165.59
163.68
141.50
132.47
117.76
113.34
112.04
78.40
55.47
34.90
33.54
31.54
24.57
22.48
13.95
CH3
O
O
O
CH3
9i
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)

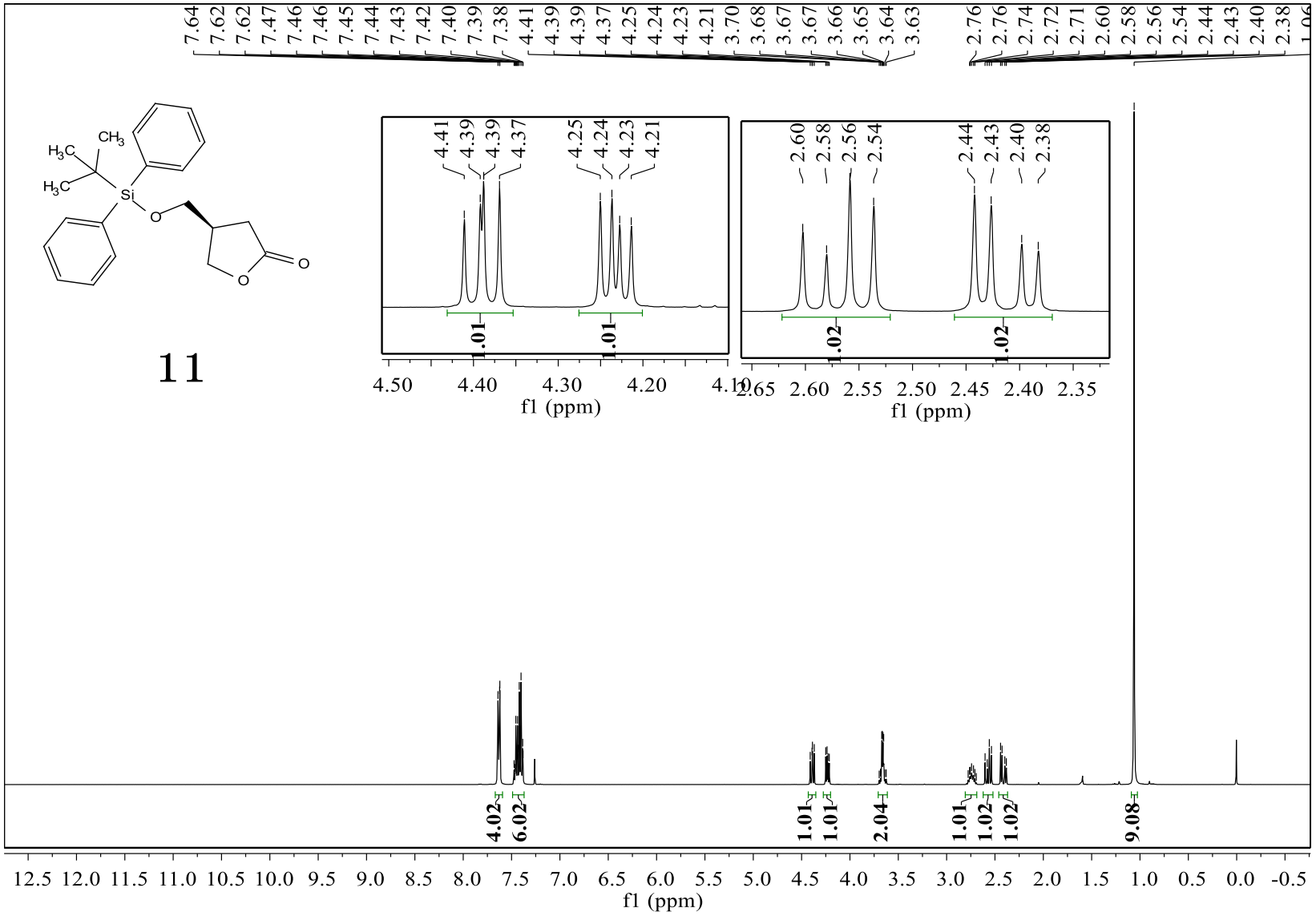

8.16 8.14 8.03 8.02 8.01 8.00 7.92 7.92 7.92 4.56 4.55 4.54 4.54 4.53 4.53 4.53 4.52 4.52 3.95 3.01 3.00 2.98 1.90 1.88 1.88 1.87 1.87 1.86 1.86 1.75 1.74 1.73 1.72 1.72 1.71 1.69 1.58 1.57 1.48 1.47 1.46 1.35 1.34 1.33 1.32 0.92 0.91 0.90 0.89 0.88
O
O
O
H3C
O
O
CH3
9j
1.00 1.00 1.02 1.04 3.30 2.14 1.05 1.14 1.14 1.25 4.29 3.44
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

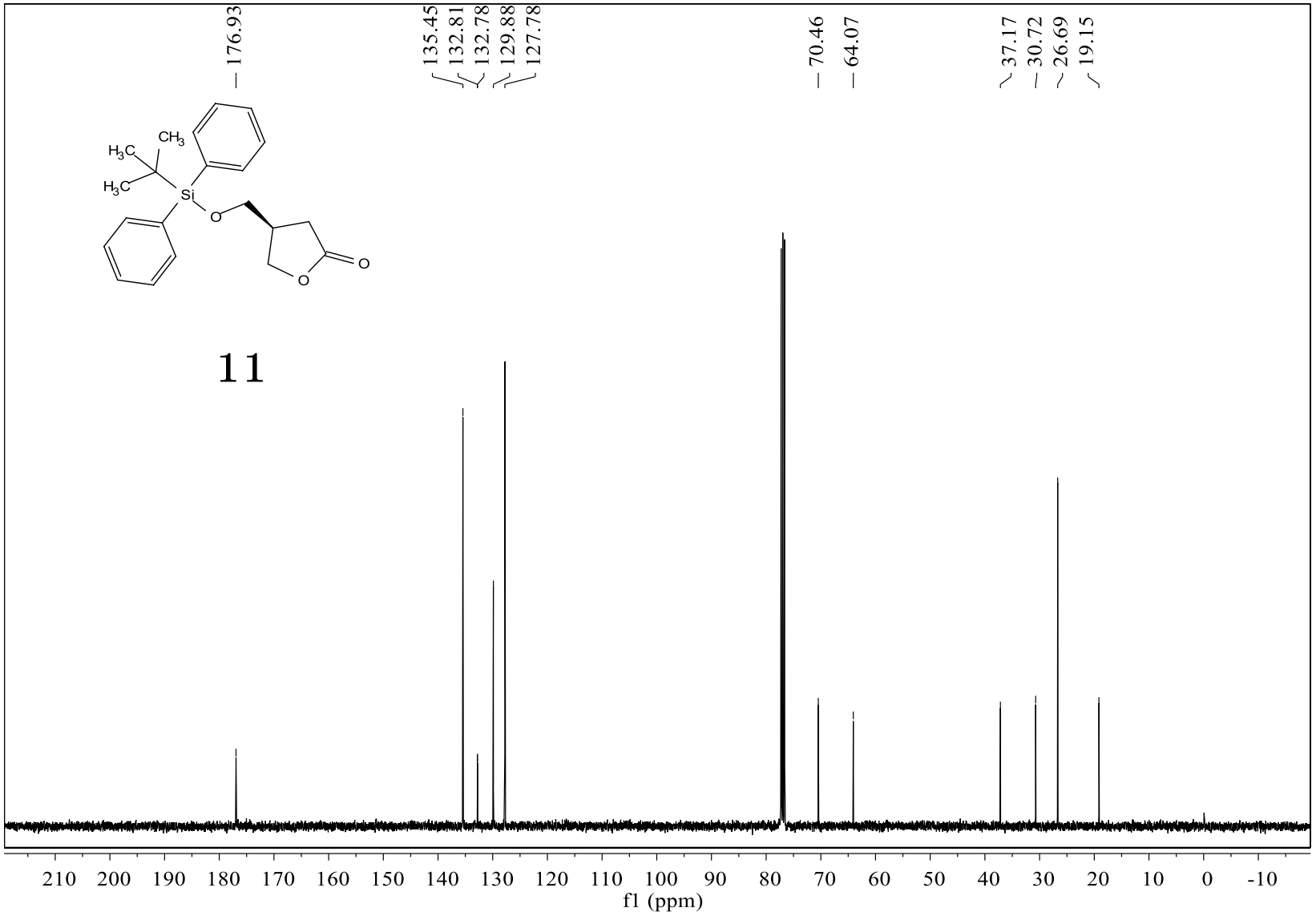

165.97
164.76
139.24
134.42
130.35
128.81
128.58
128.42
78.90
52.56
34.84
33.08
31.50
24.55
22.49
13.96
O
O
O
O
H3C
CH3
9j
f1 (ppm)

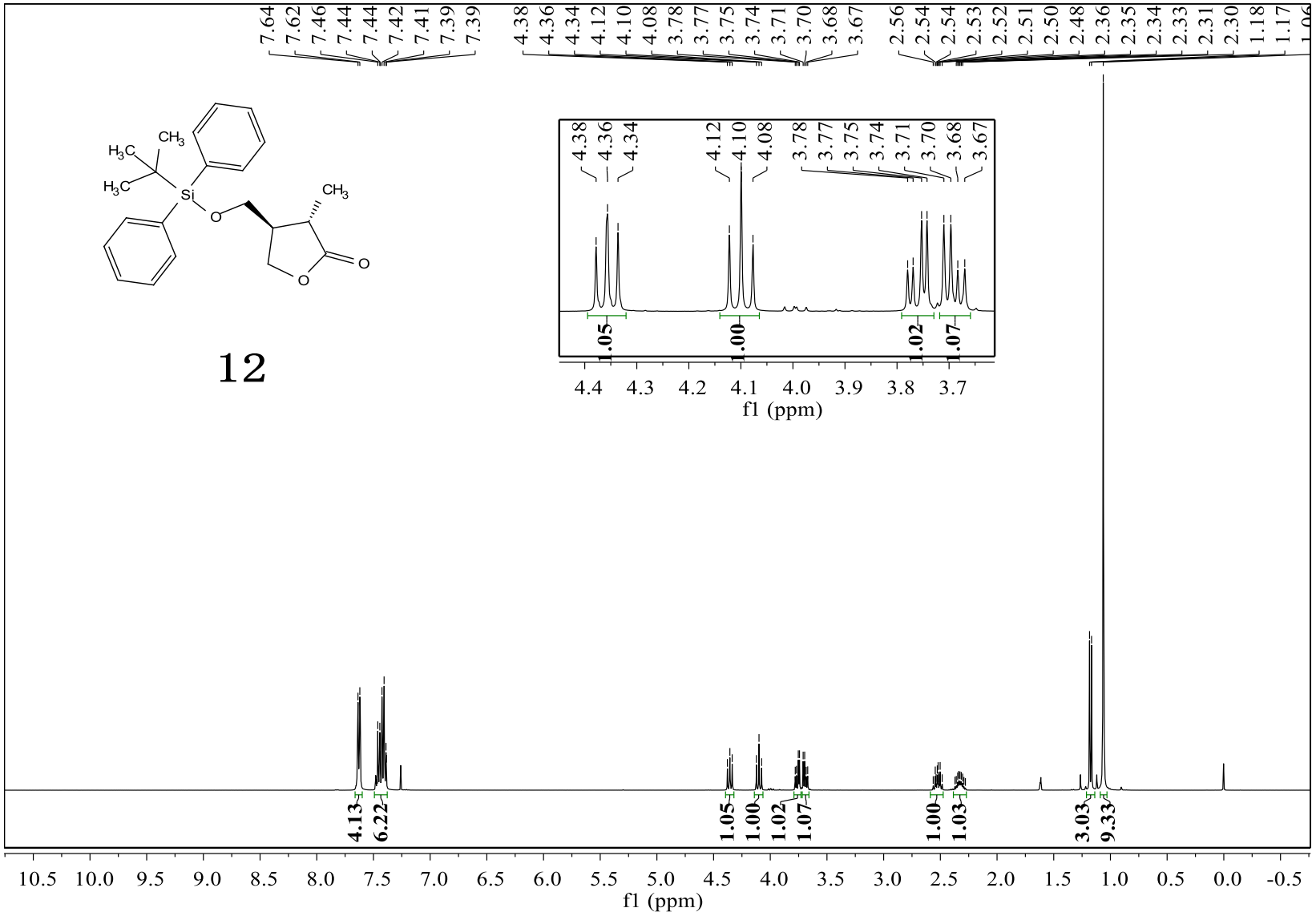

8.12 8.11 8.10 8.08 7.08 7.07 7.06 7.05 7.04 7.03 6.94 6.93 6.92 6.91
4.52 4.51 4.50 2.97 2.94 2.91 2.90 2.87 2.86 1.87 1.85 1.84 1.74 1.72 1.71 1.70 1.70 1.69 1.68 1.56 1.47 1.46 1.45 1.45 1.34 1.33 1.32 1.31 1.31 1.30 0.91 0.91 0.90 0.90 0.88 0.88
O
O
F
CH3
9k
1.00
1.00
1.00
1.03
2.12
1.05
1.11
1.01
1.14
4.36
3.40
f1 (ppm)

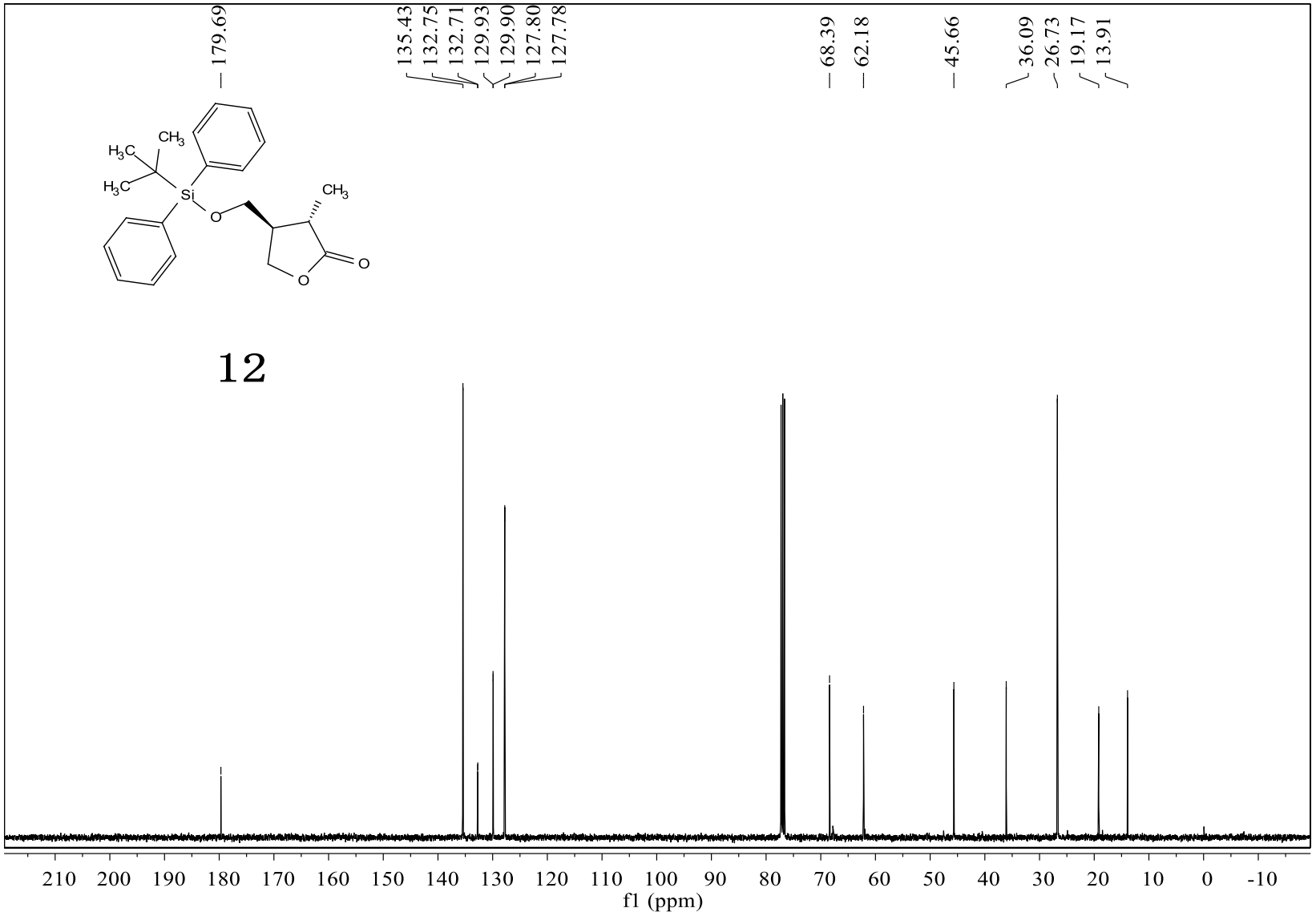

166.99
164.69
164.44
142.26
142.17
133.24
133.14
121.56
121.53
115.21
114.99
114.28
114.06
78.55
34.82
33.28
31.49
24.51
22.46
13.94
O
O
F
CH3
9k
f1 (ppm)
f1 (ppm)
f1 (ppm)

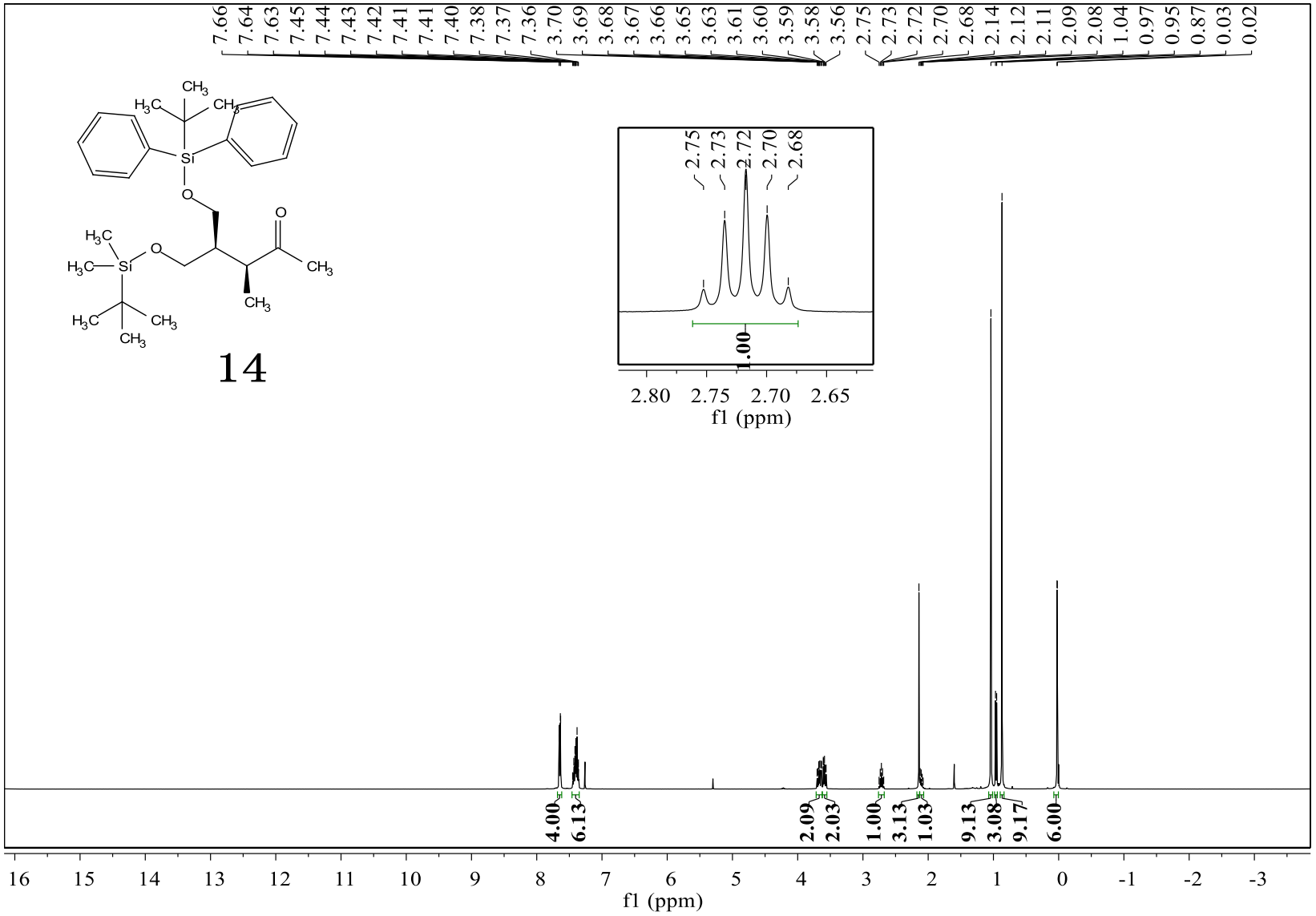

-103.9
O
O
F
CH3
19F−9k
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

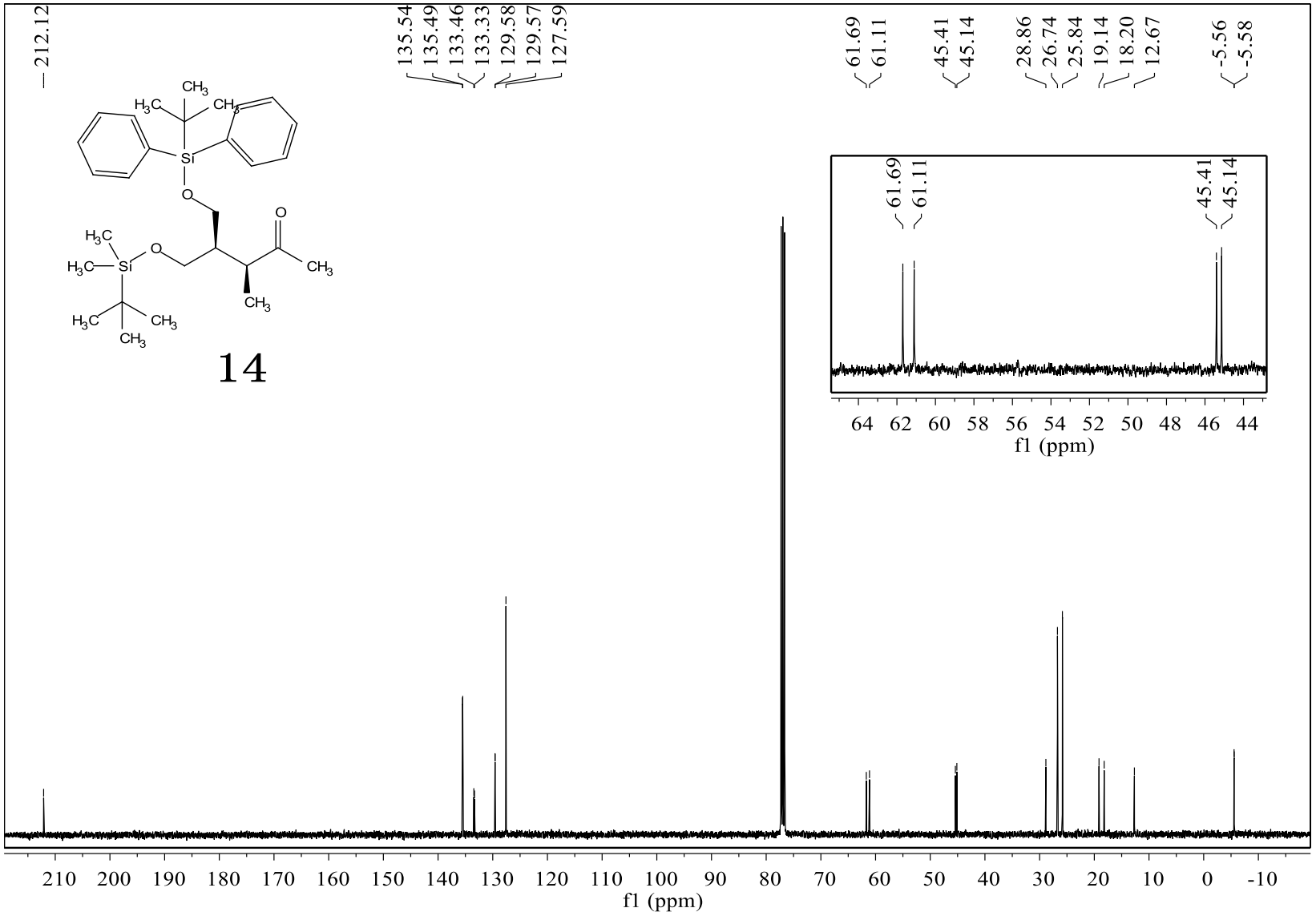

11
f1 (ppm)
f1 (ppm)
f1 (ppm)

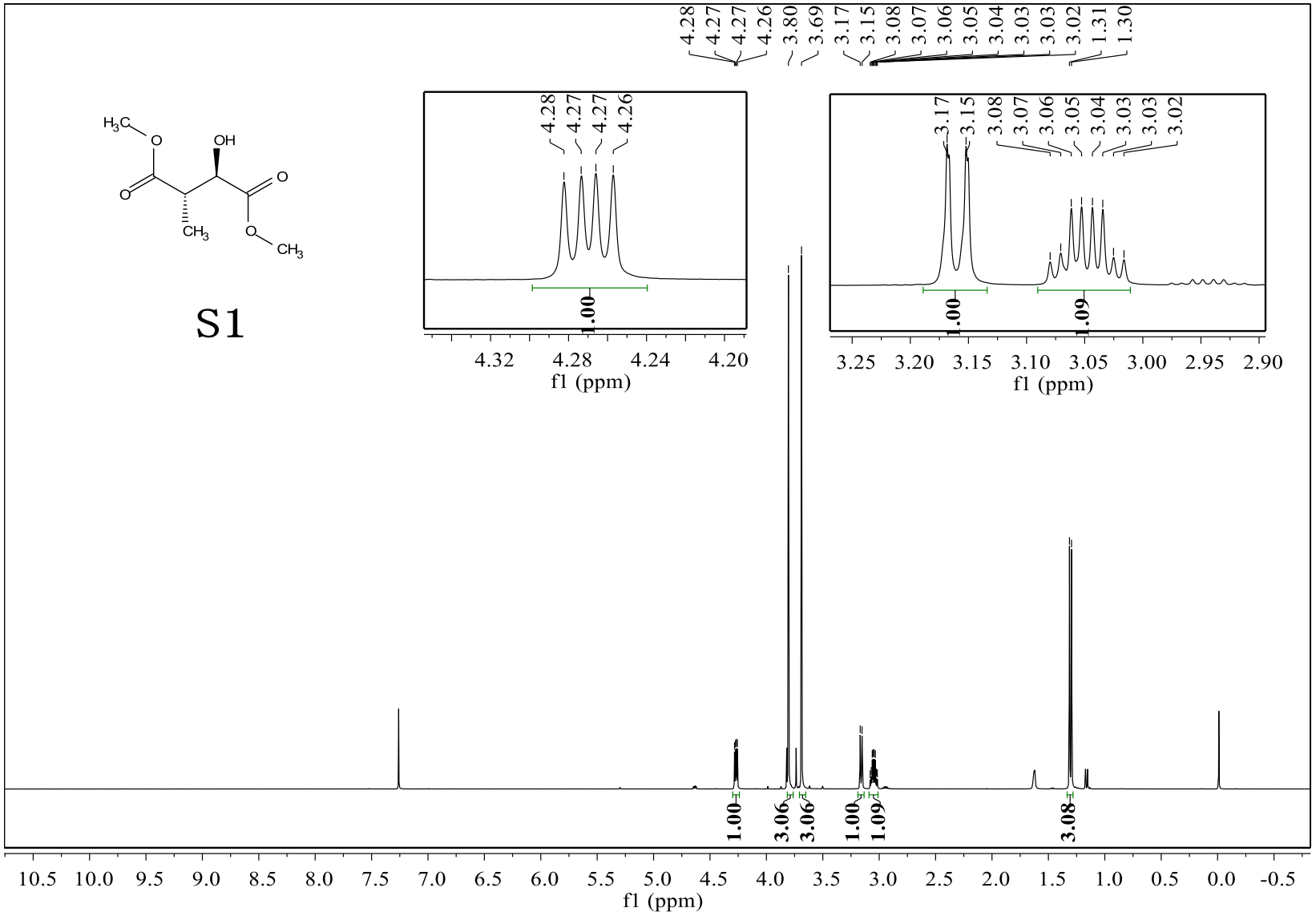

176.93
135.45
132.81
132.78
129.88
127.78
70.46
64.07
37.17
30.72
26.69
19.15
CH3
H3C
H3C
Si
O
O
O
11
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

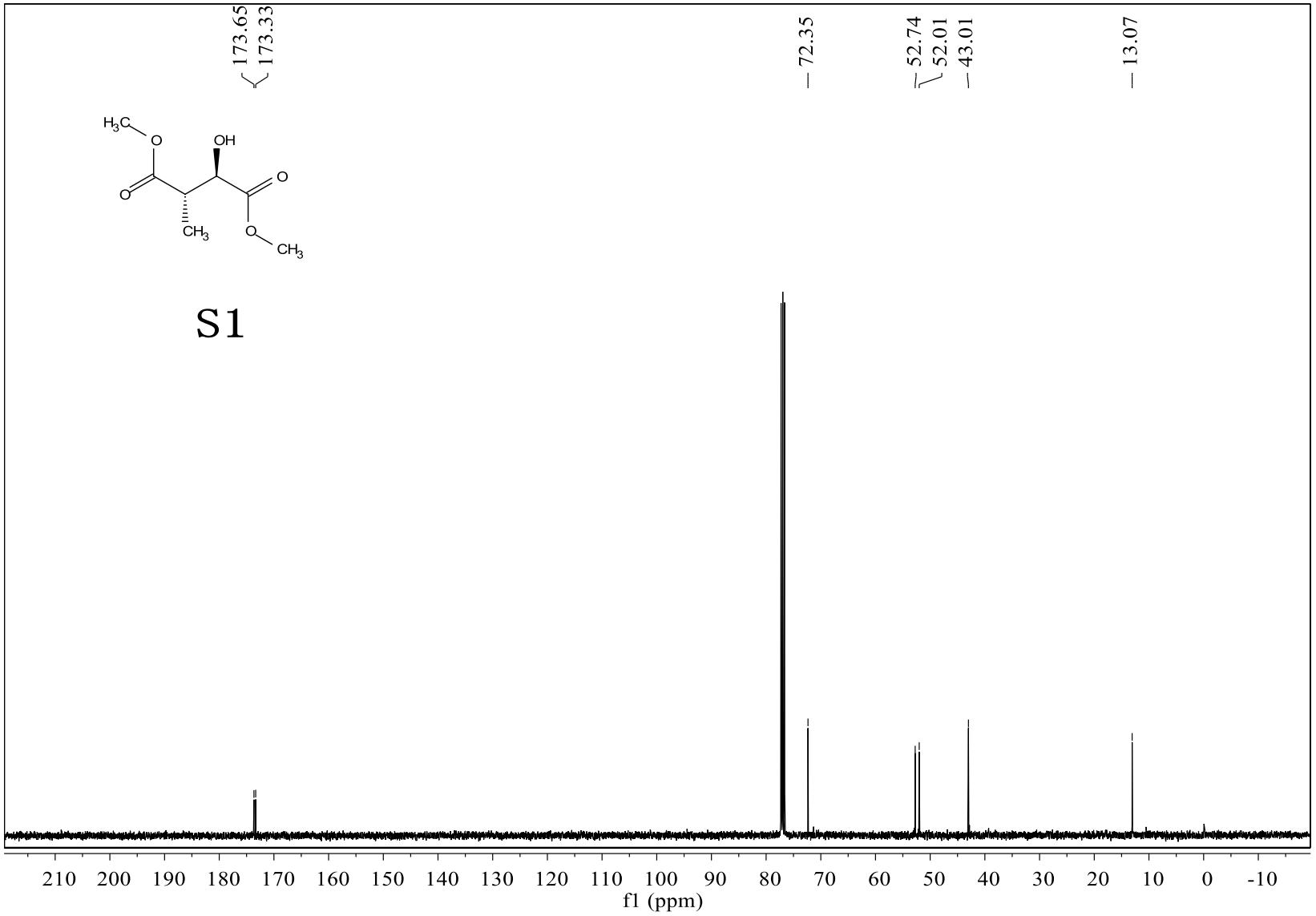

12
f1 (ppm)
f1 (ppm)

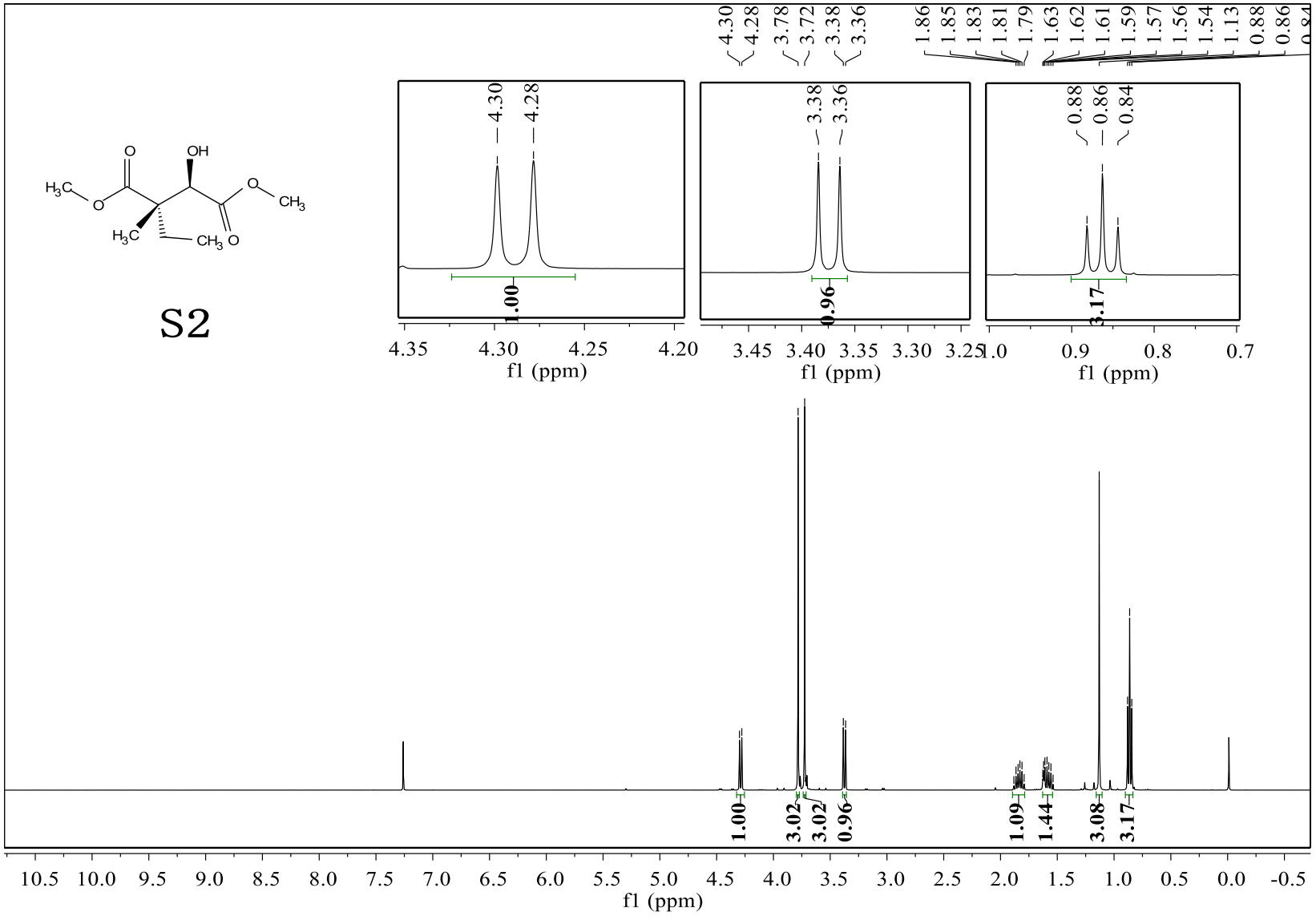

179.69
135.43
132.75
132.71
129.93
129.90
127.80
127.78
68.39
62.18
45.66
36.09
26.73
19.17
13.91
12
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

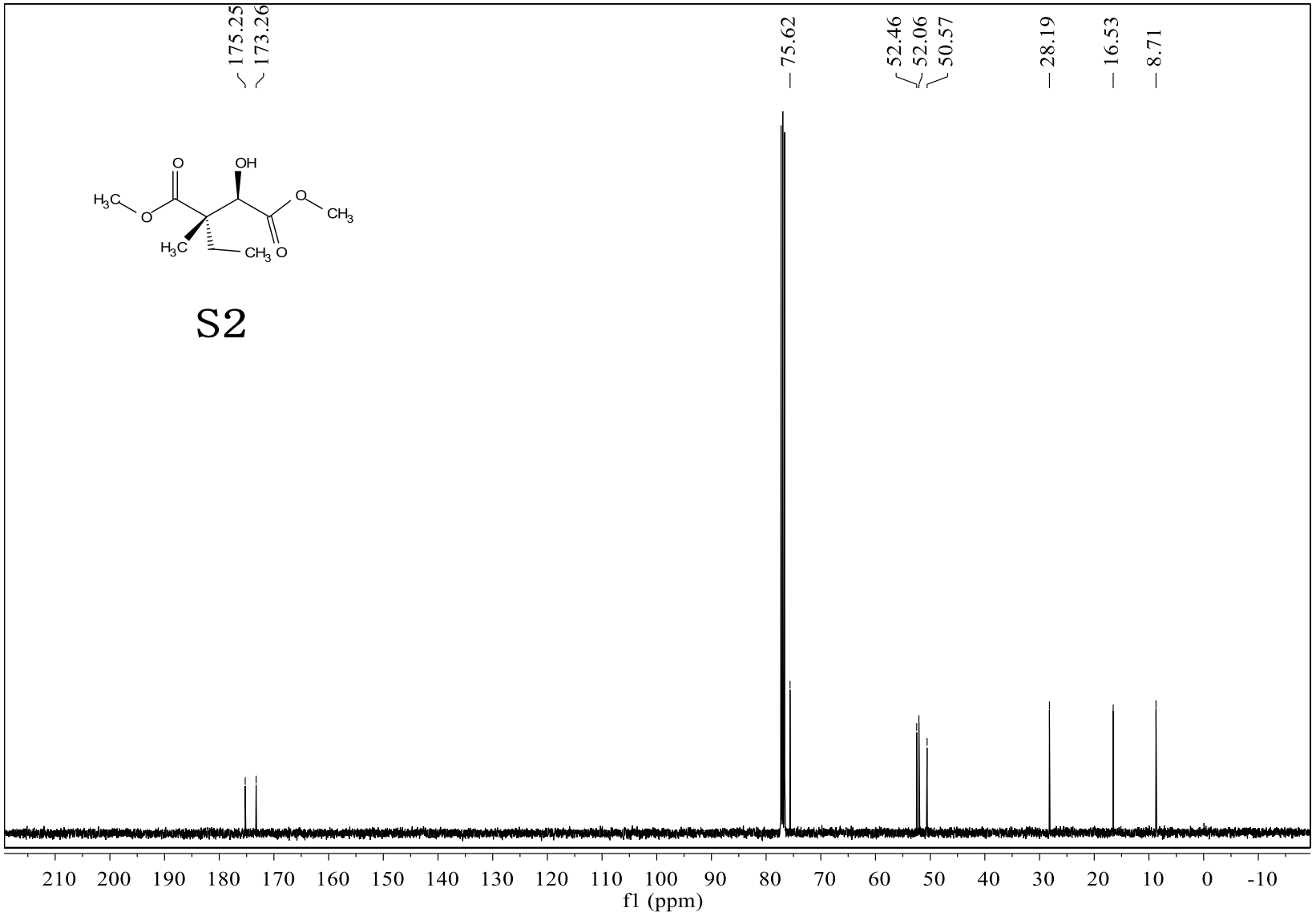

7.66 7.64 7.63 7.45 7.44 7.43 7.42 7.41 7.41 7.40 7.38 7.37 7.36 3.70 3.69 3.68 3.67 3.66 3.65 3.63 3.61 3.60 3.59 3.58 3.56 2.75 2.73 2.72 2.70 2.68 2.14 2.12 2.11 2.09 2.08 1.04 0.97 0.95 0.87 0.03 0.02
14
2.75 2.73 2.72 2.70 2.68
1.00
2.80 2.75 2.70 2.65
f1 (ppm)
4.00 6.13 2.09 2.03 1.00 3.13 1.03 9.13 3.08 9.17 6.00
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)

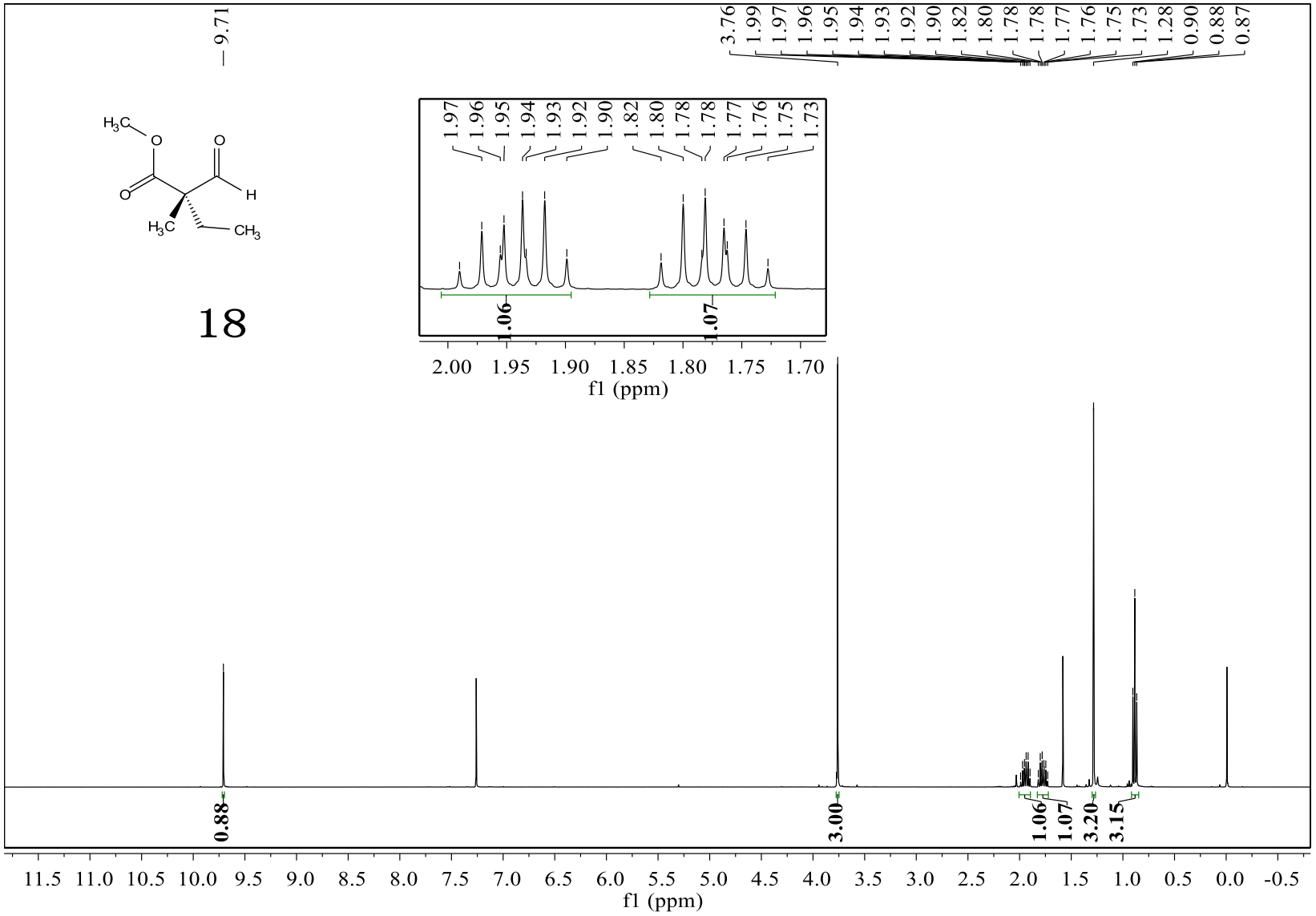

212.12
135.54
135.49
133.46
133.33
129.58
129.57
127.59
61.69
61.11
45.41
45.14
28.86
26.74
25.84
19.14
18.20
12.67
-5.56
-5.58
14
f1 (ppm)
f1 (ppm)

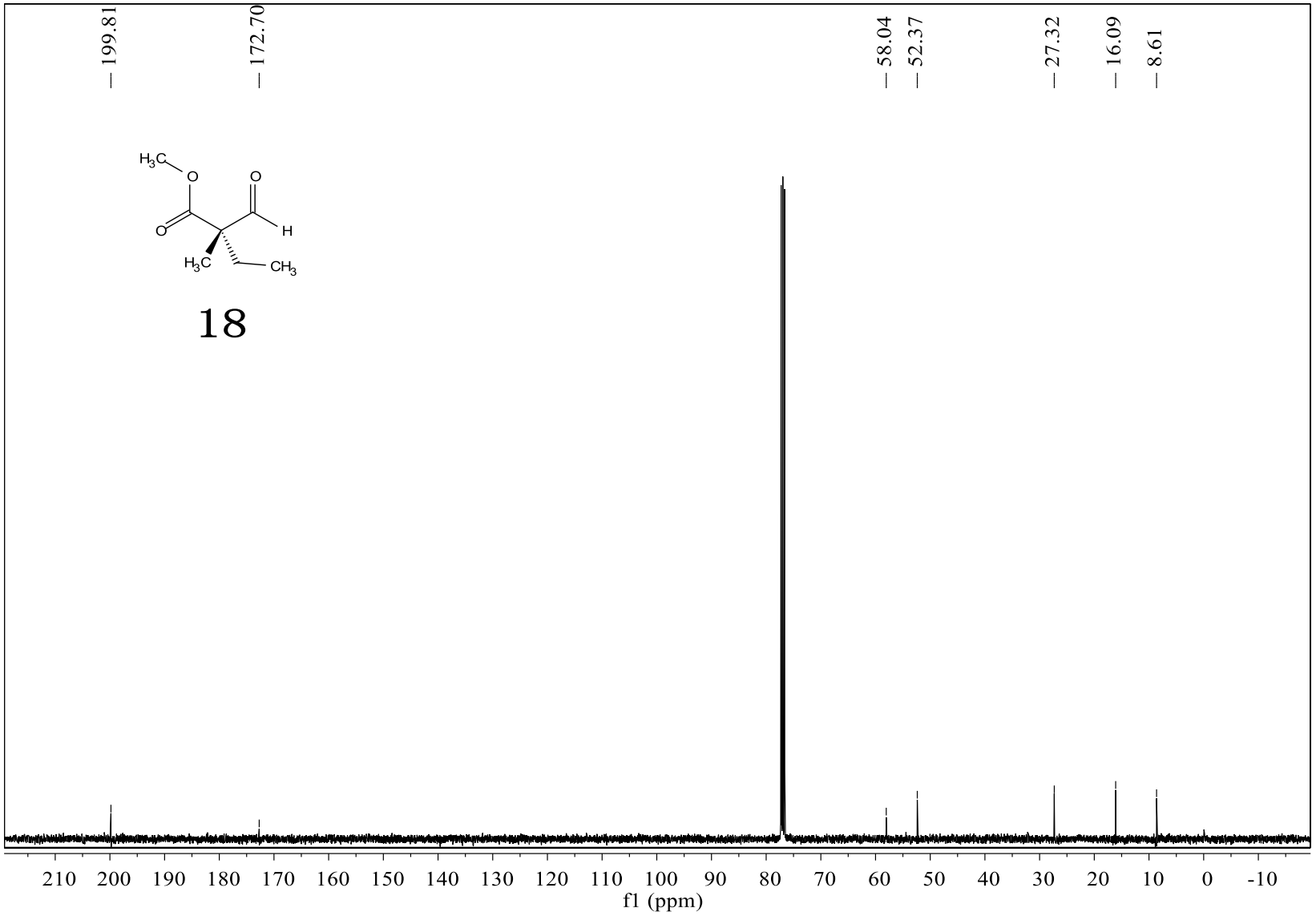

4.28
4.27
4.27
4.26
3.80
3.69
3.17
3.15
3.08
3.07
3.06
3.05
3.04
3.03
3.03
3.02
1.31
1.30
H3C
O
OH
O
O
CH3
O
CH3
S1
1.00
4.32
4.28
4.24
4.20
f1 (ppm)
1.00
1.09
3.25
3.20
3.15
3.10
3.05
3.00
2.95
2.90
f1 (ppm)
1.00
3.06
3.06
1.00
1.09
3.08
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

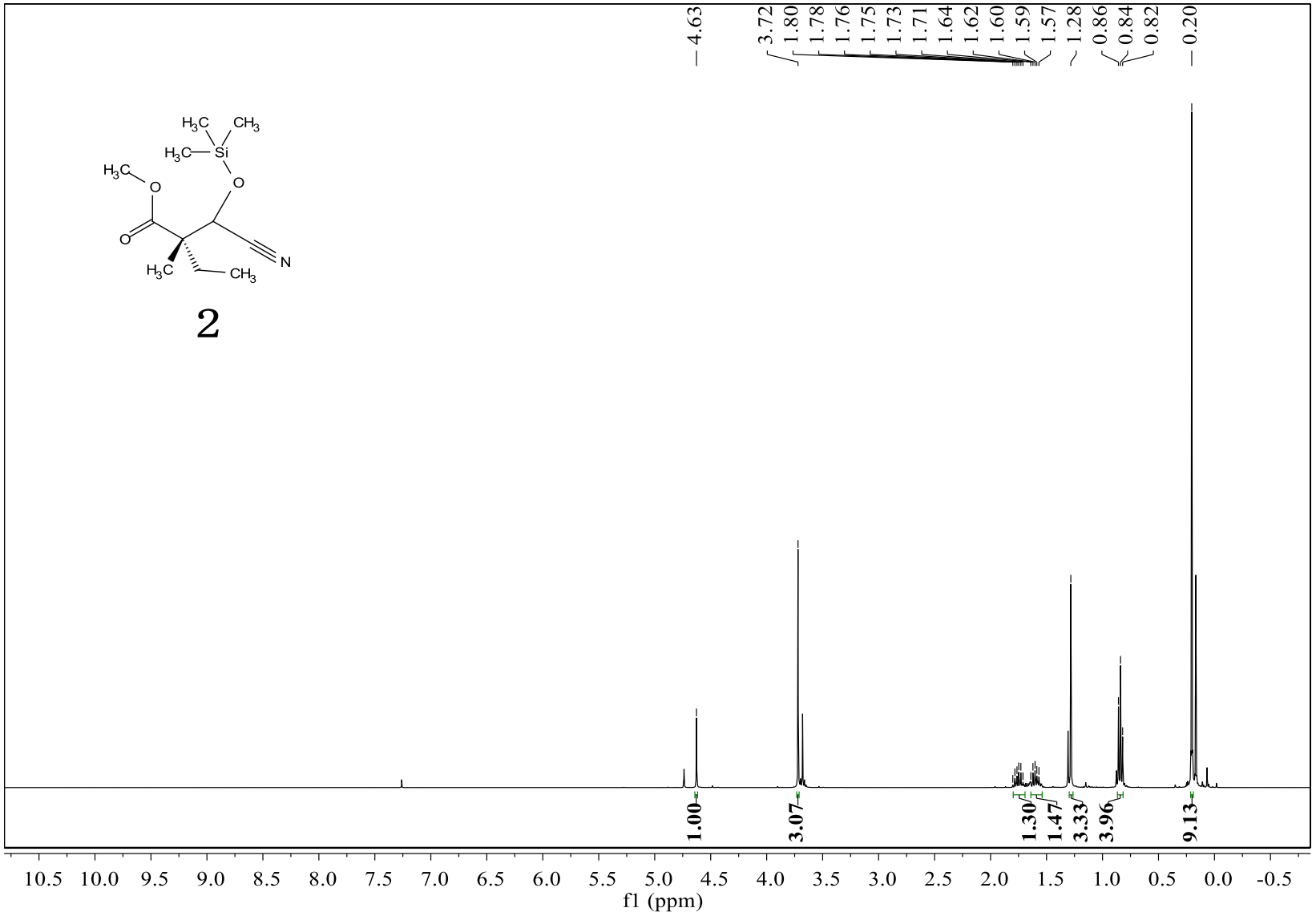

173.65
173.33
72.35
52.74
52.01
43.01
13.07
H3C
O
OH
O
O
CH3
O
CH3
S1
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


S2
4.30
4.28
3.78
3.72
3.38
3.36
1.86
1.85
1.83
1.81
1.79
1.63
1.62
1.61
1.59
1.57
1.56
1.54
1.13
0.88
0.86
1.00
0.96
3.17
f1 (ppm)
1.00
3.02
3.02
0.96
1.09
1.44
3.08
3.17

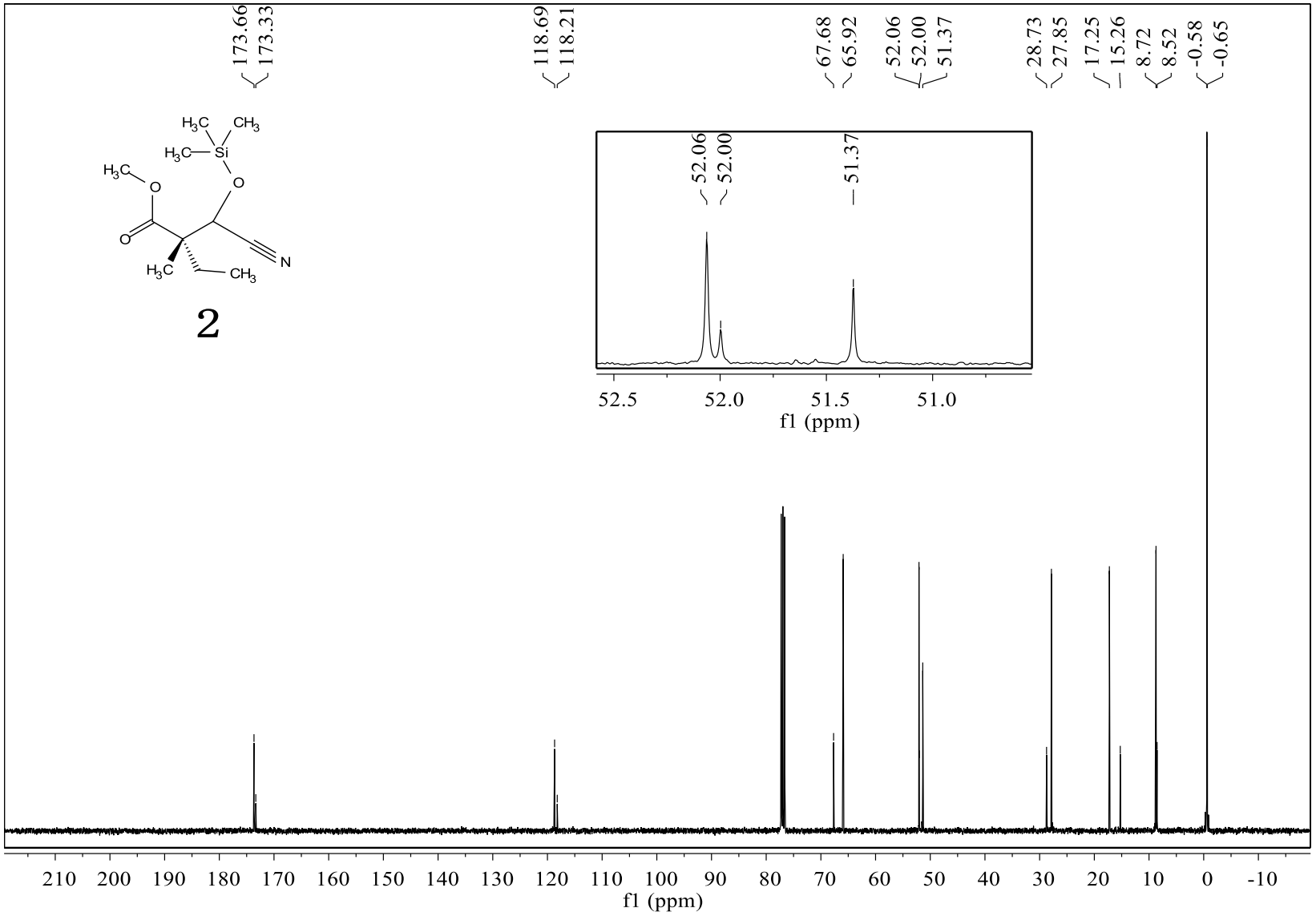

175.25
173.26
75.62
52.46
52.06
50.57
28.19
16.53
8.71
O
OH
H3C
O
O
CH3
H3C
CH3
O
S2
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


9.71
3.76
1.99
1.97
1.96
1.95
1.94
1.93
1.92
1.90
1.82
1.80
1.78
1.78
1.77
1.76
1.75
1.73
1.28
0.90
0.88
0.87
H3C
O
O
O
H
H3C
CH3
18
1.06
1.07
2.00 1.95 1.90 1.85 1.80 1.75 1.70
f1 (ppm)
0.88
3.00
1.06
1.07
3.20
3.15
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

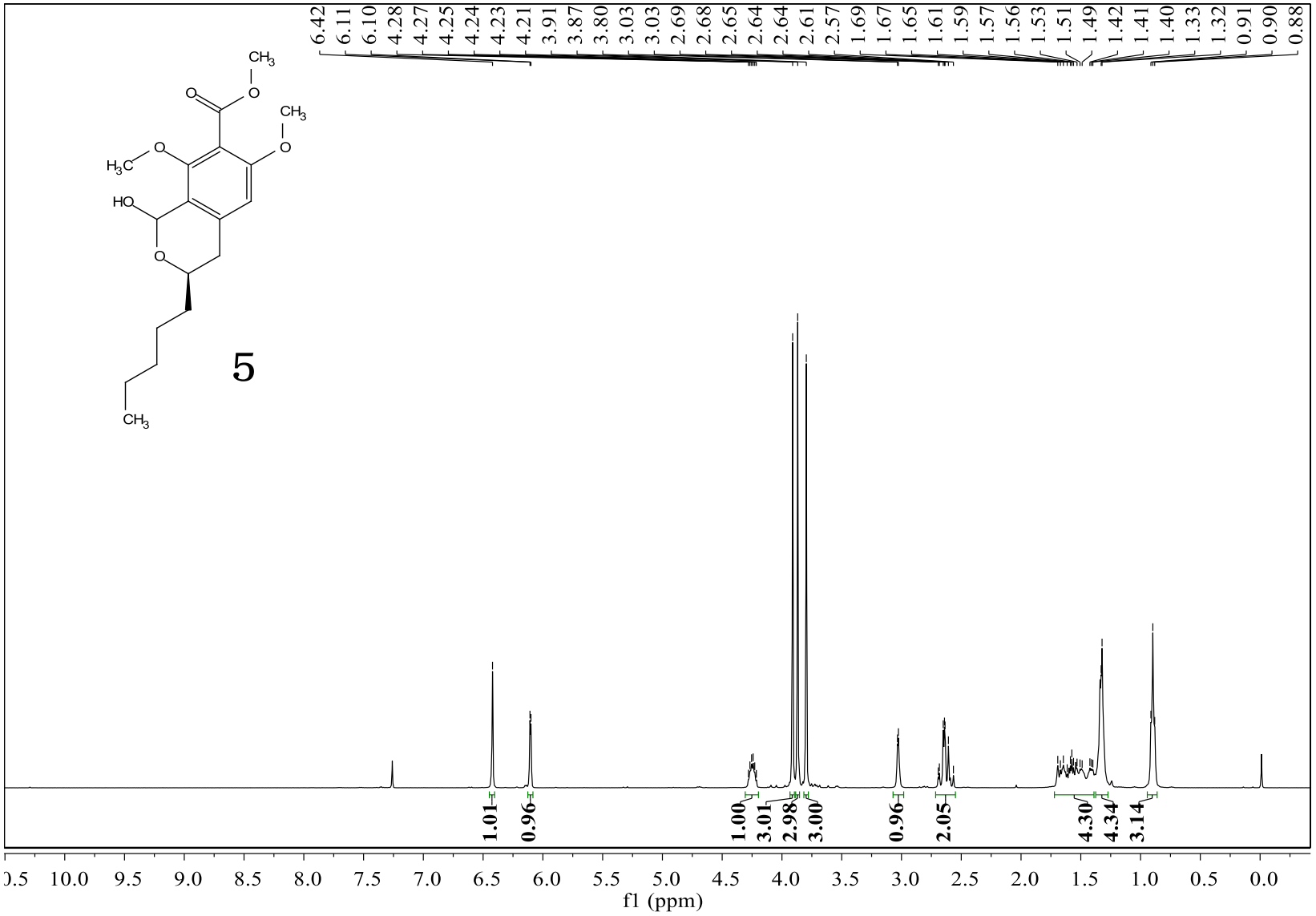

199.81
172.70
58.04
52.37
27.32
16.09
8.61
H3C
O
O
O
H
H3C
CH3
18
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

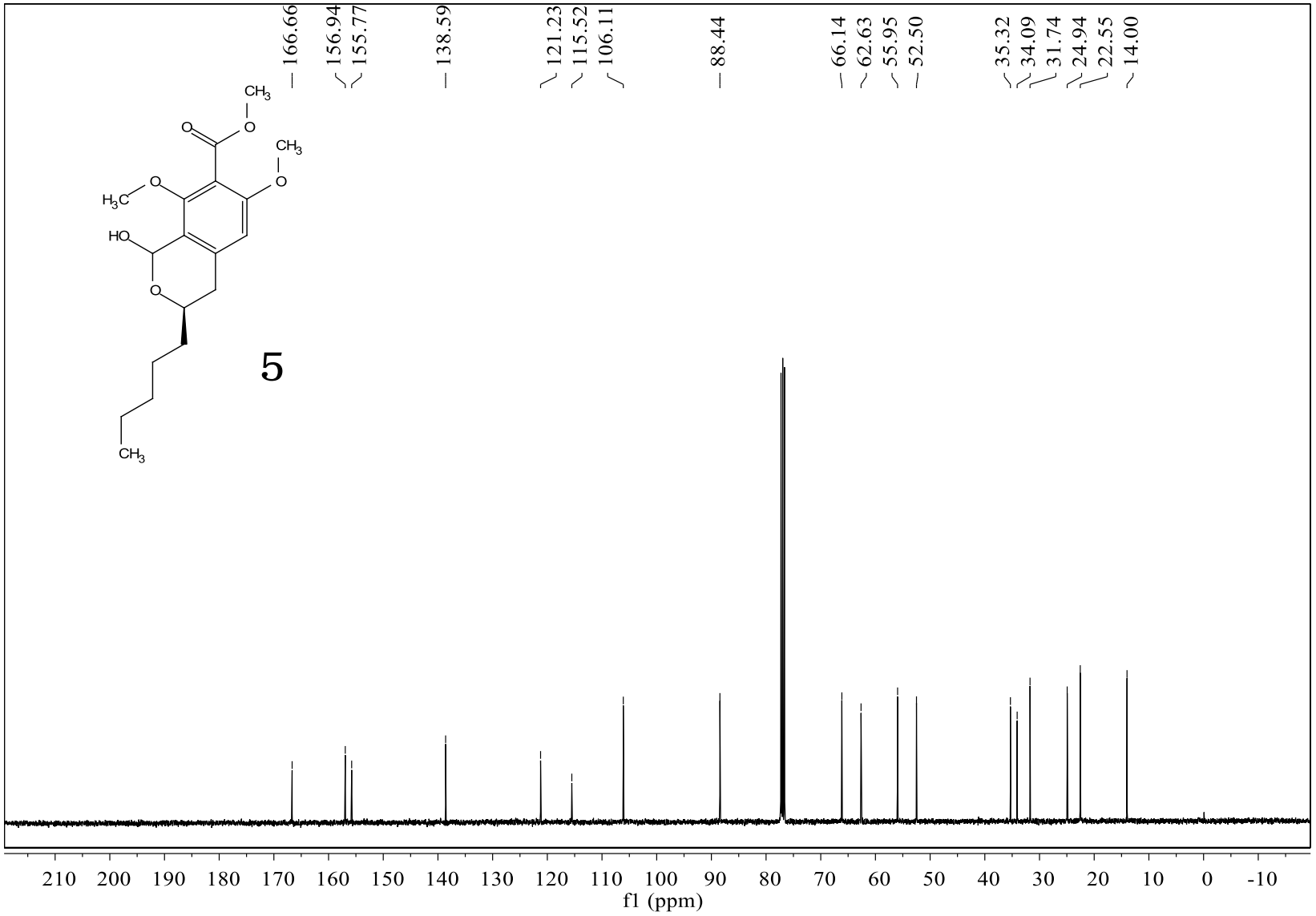

4.63
3.72
1.80
1.78
1.76
1.75
1.73
1.71
1.64
1.62
1.60
1.59
1.57
1.28
0.86
0.84
0.82
0.20
1.00
3.07
1.30
1.47
3.33
3.96
9.13
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

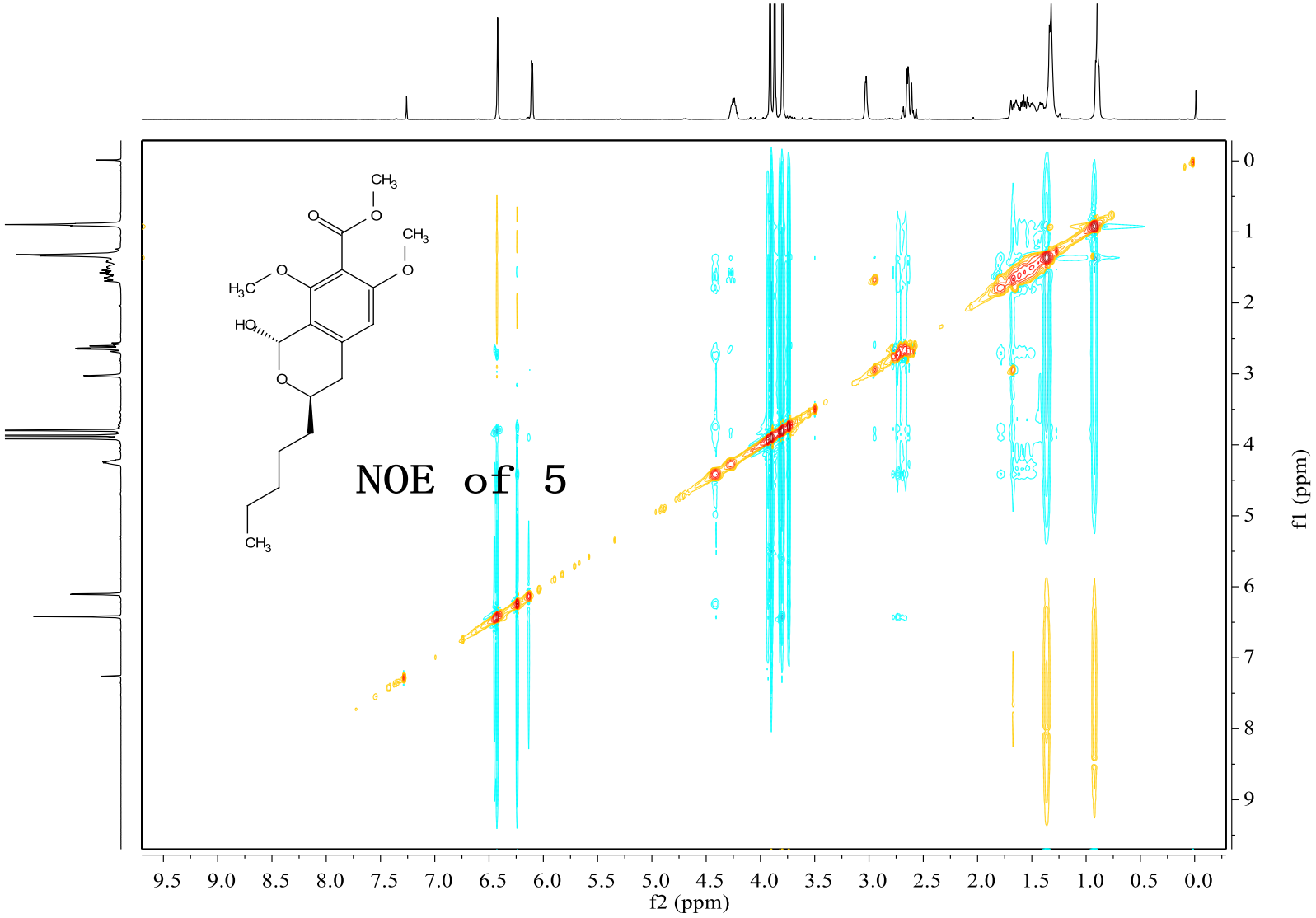
2

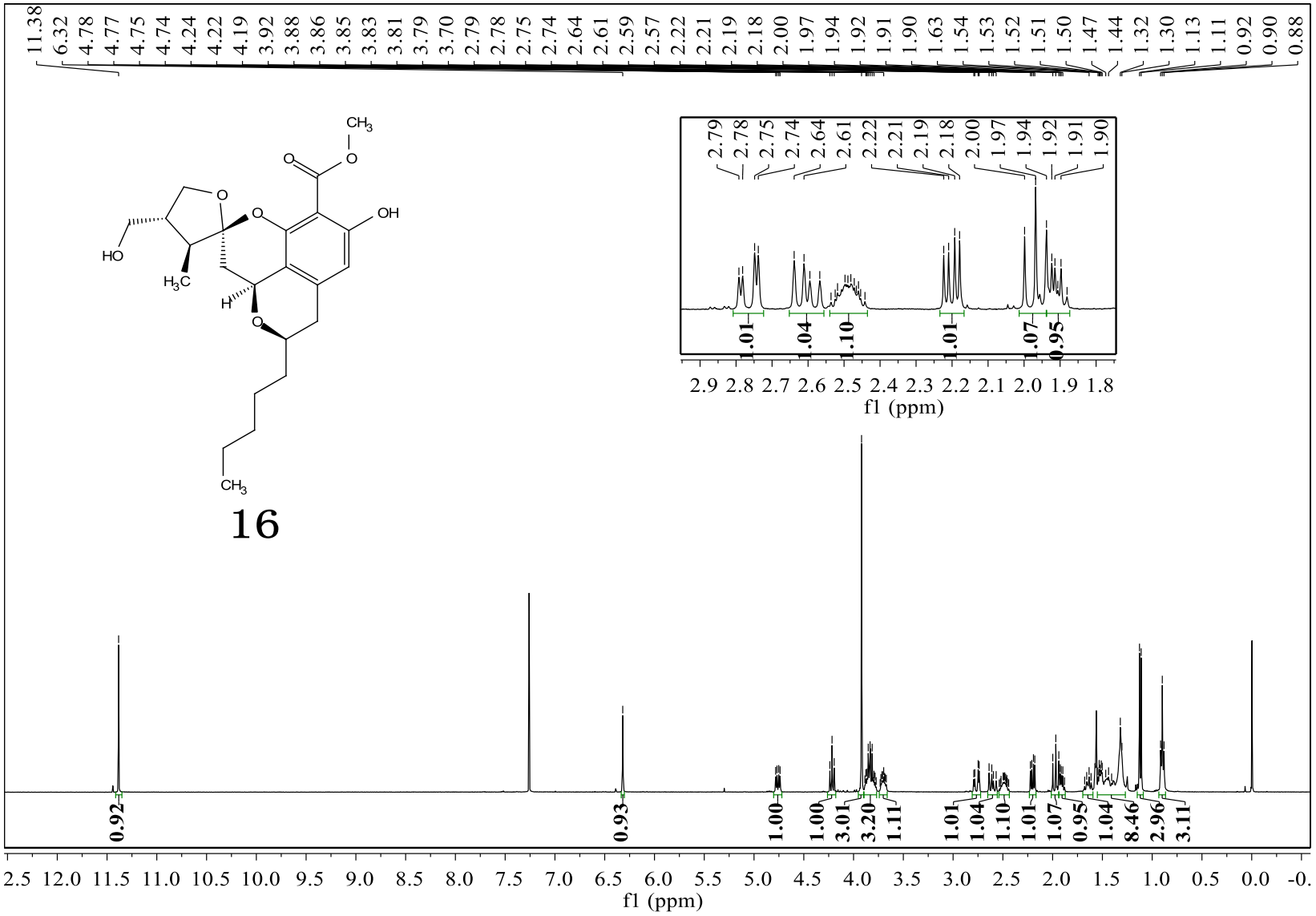

173.66
173.33
118.69
118.21
67.68
65.92
52.06
52.00
51.37
28.73
27.85
17.25
15.26
8.72
8.52
-0.58
-0.65
52.06
52.00
51.37
52.5
52.0
51.5
51.0
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

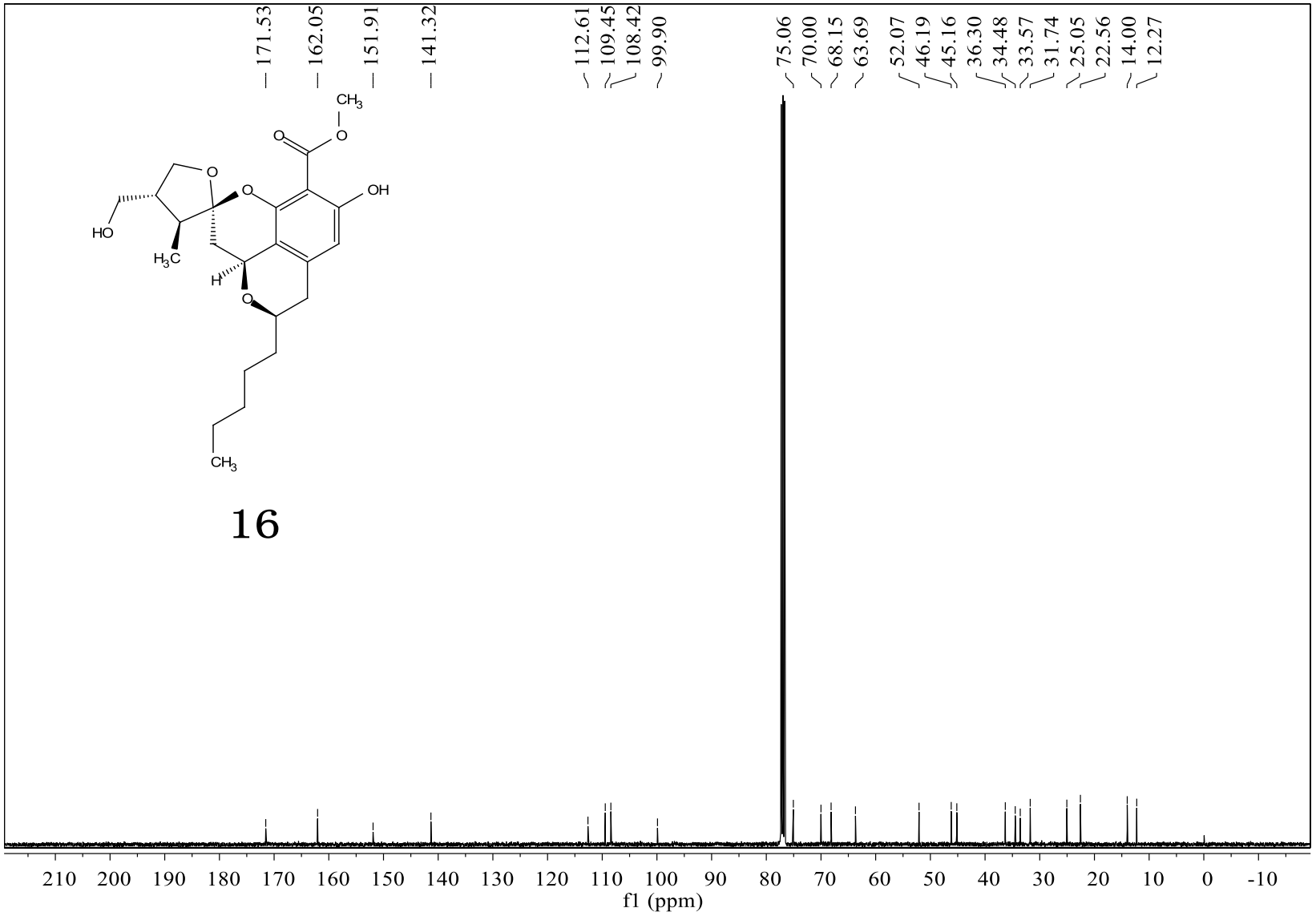
2

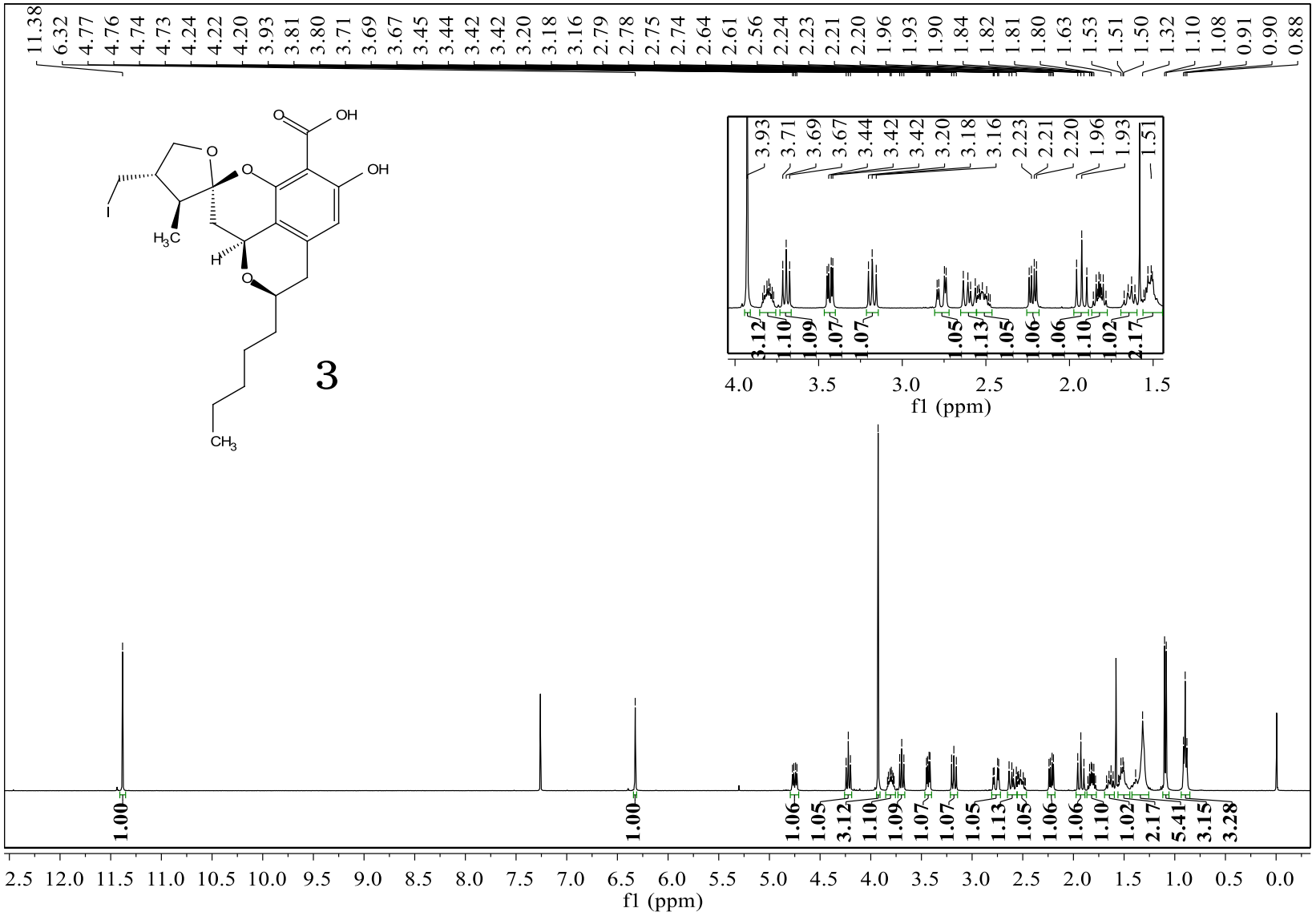

6.42
6.11
6.10
4.28
4.27
4.25
4.24
4.23
4.21
3.91
3.87
3.80
3.03
3.03
2.69
2.68
2.65
2.64
2.64
2.61
2.57
1.69
1.67
1.65
1.61
1.59
1.57
1.56
1.53
1.51
1.49
1.42
1.41
1.40
1.33
1.32
0.91
0.90
0.88
CH3
O
O
CH3
O
H3C
O
HO
O
CH3
5
1.01
0.96
1.00
3.01
2.98
3.00
0.96
2.05
4.30
4.34
3.14
f1 (ppm)

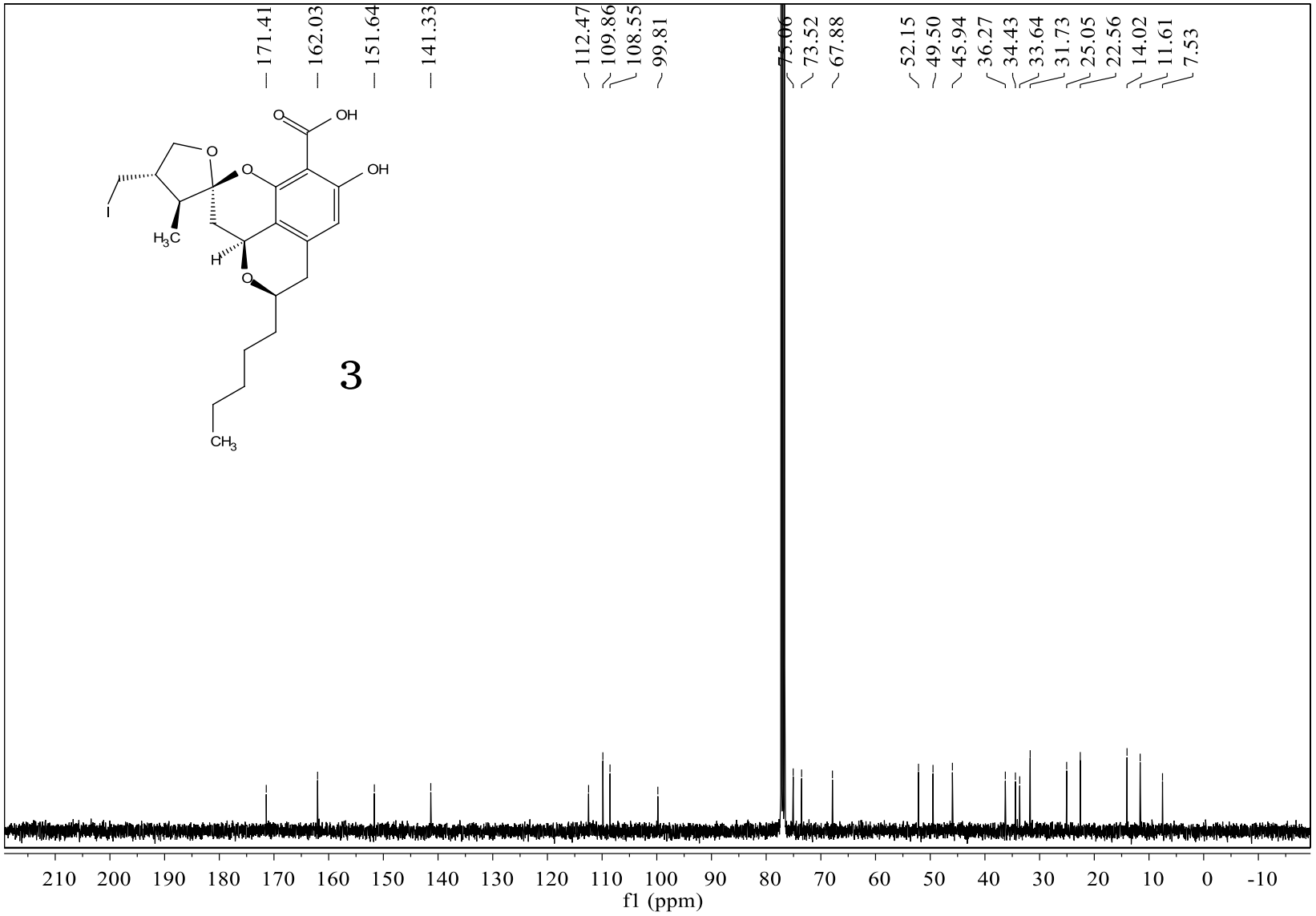

166.66
156.94
155.77
138.59
121.23
115.52
106.11
88.44
66.14
62.63
55.95
52.50
35.32
34.09
31.74
24.94
22.55
14.00
5
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

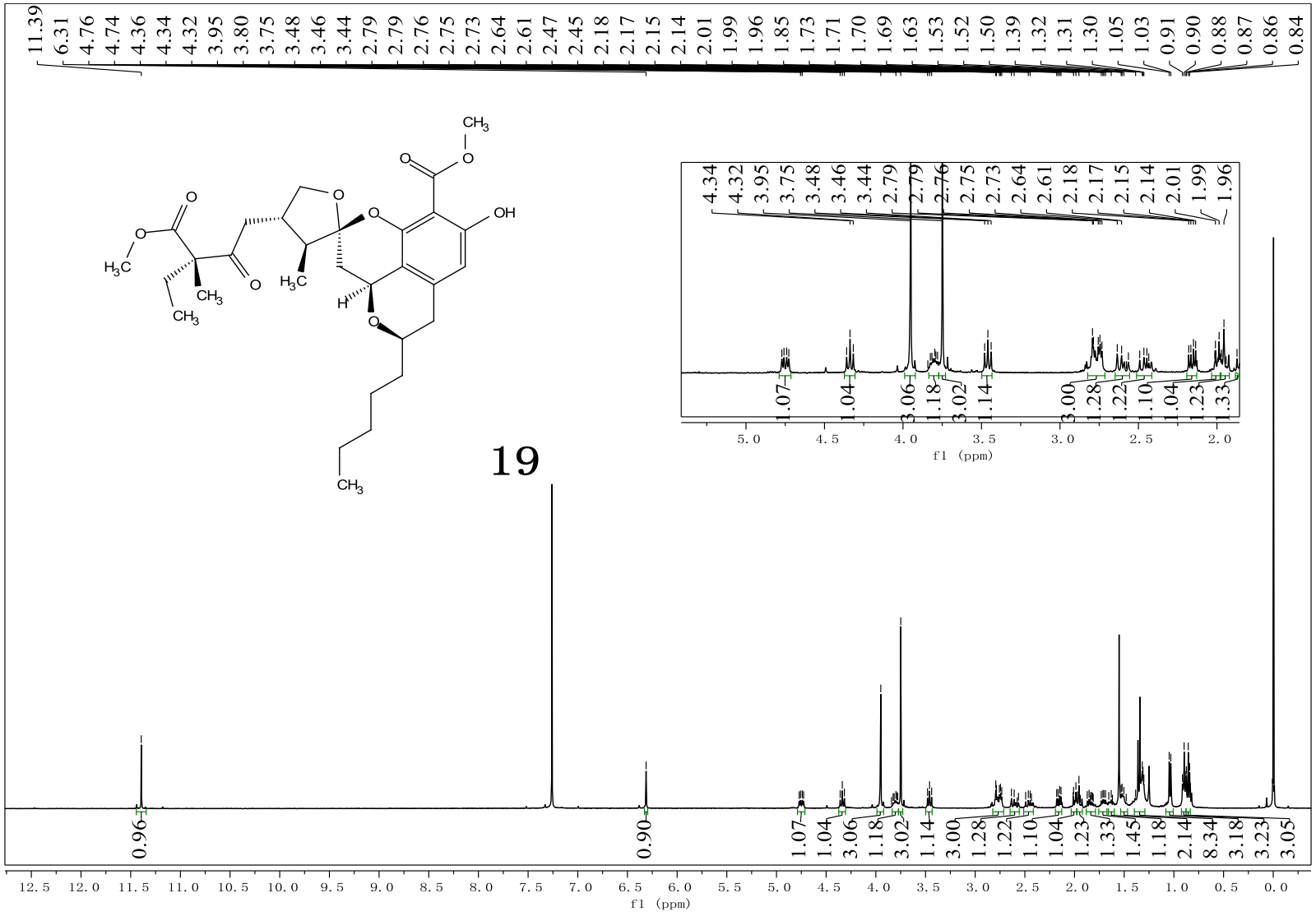

NOE of 5
f2 (ppm)
f1 (ppm)

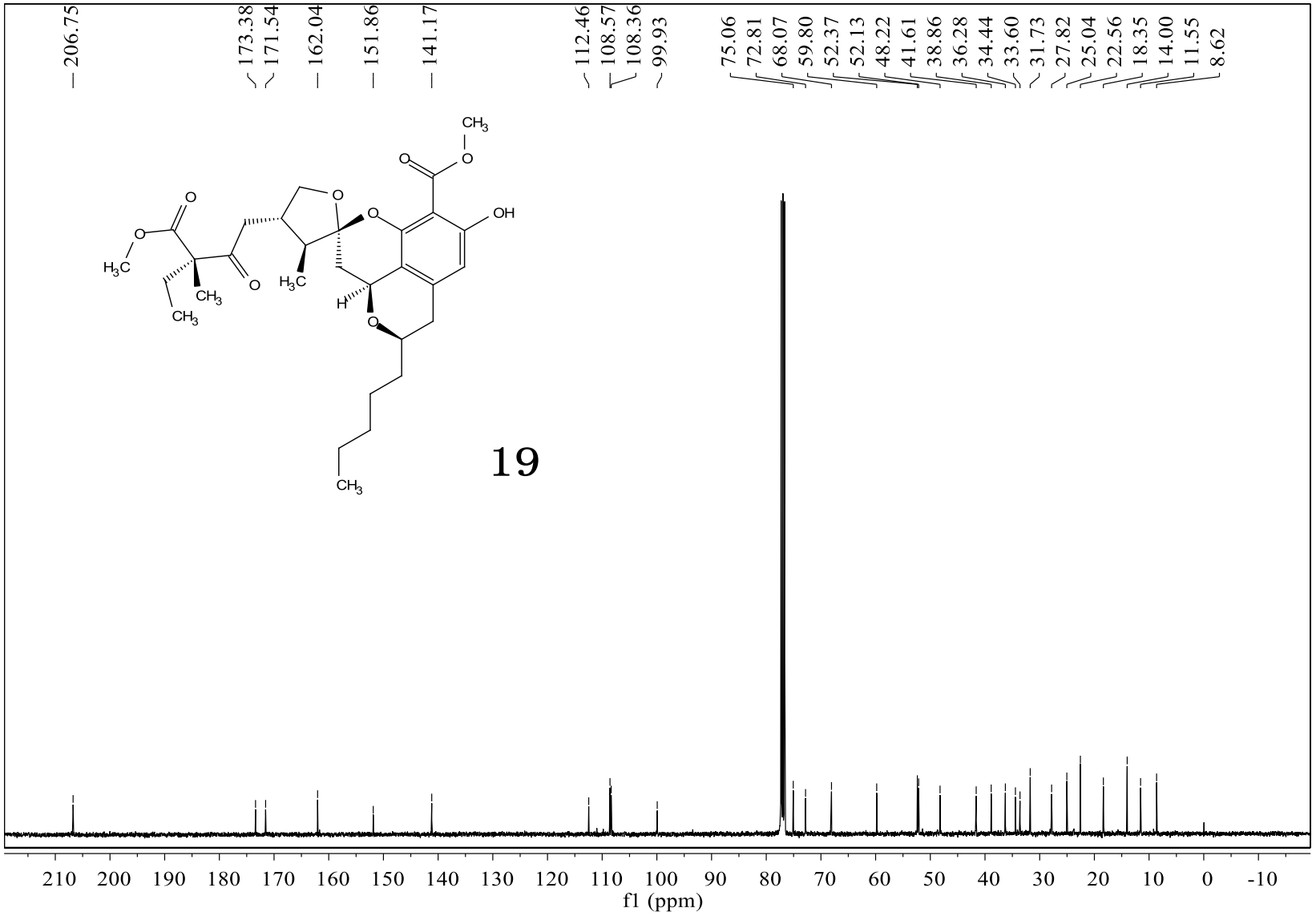

11.38 6.32 4.78 4.77 4.75 4.74 4.24 4.22 4.19 3.92 3.88 3.86 3.85 3.83 3.81 3.79 3.70 2.79 2.78 2.75 2.74 2.64 2.61 2.59 2.57 2.22 2.21 2.19 2.18 2.00 1.97 1.94 1.92 1.91 1.90 1.63 1.54 1.53 1.52 1.51 1.50 1.47 1.44 1.32 1.30 1.13 1.11 0.92 0.90 0.88
CH3
O
O
O
O
OH
HO
H3C
H
O
CH3
16
2.79 2.78 2.75 2.74 2.64 2.61 2.22 2.21 2.19 2.18 2.00 1.97 1.94 1.92 1.91 1.90
1.01 1.04 1.10 1.01 1.07 0.95
2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8
f1 (ppm)
0.92 0.93 1.00 1.00 3.01 3.20 1.11 1.01 1.04 1.10 1.01 1.07 0.95 1.04 8.46 2.96 3.11
2.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.
f1 (ppm)

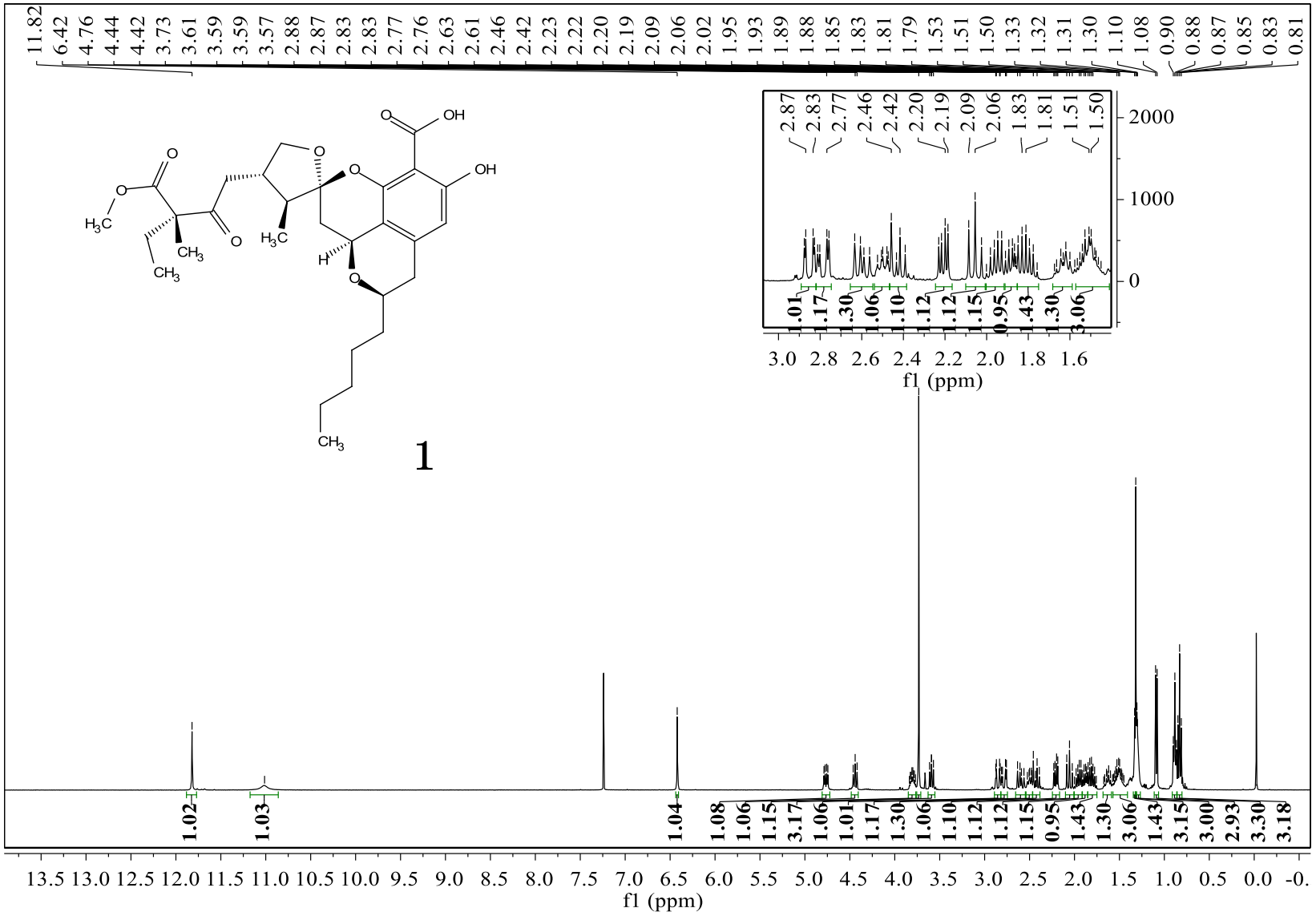

171.53
162.05
151.91
141.32
112.61
109.45
108.42
99.90
75.06
70.00
68.15
63.69
52.07
46.19
45.16
36.30
34.48
33.57
31.74
25.05
22.56
14.00
12.27
CH3
O
O
O
O
OH
HO
H3C
H
O
CH3
16
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

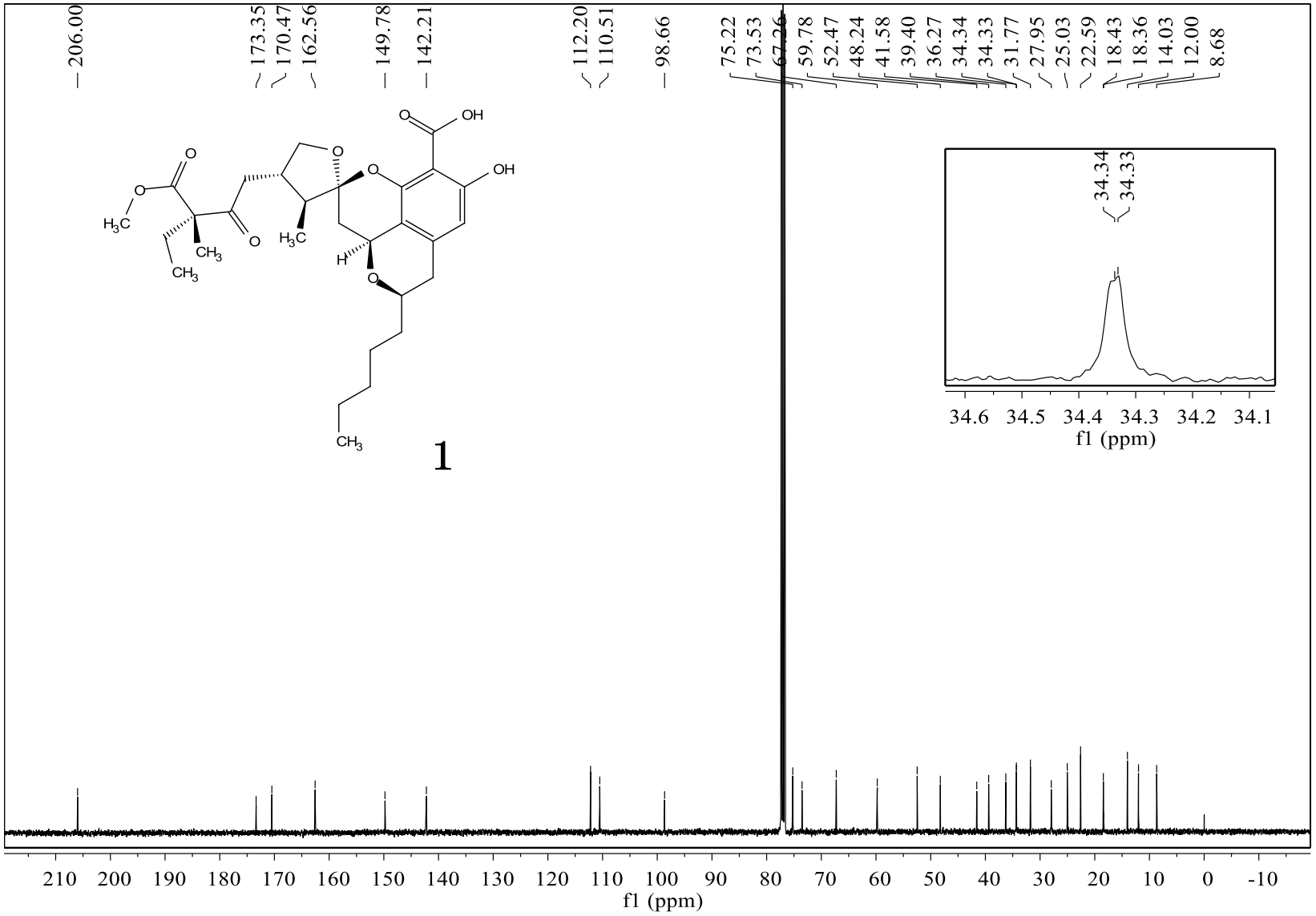

11.38 6.32 4.77 4.76 4.74 4.73 4.24 4.22 4.20 3.93 3.81 3.80 3.71 3.69 3.67 3.45 3.44 3.42 3.42 3.20 3.18 3.16 2.79 2.78 2.75 2.74 2.64 2.61 2.56 2.24 2.23 2.21 2.20 1.96 1.93 1.90 1.84 1.82 1.81 1.80 1.63 1.53 1.51 1.50 1.32 1.10 1.08 0.91 0.90 0.88
O
OH
O
O
OH
H3C
H
O
CH3
3
3.93 3.71 3.69 3.67 3.44 3.42 3.42 3.20 3.18 3.16 2.23 2.21 2.20 1.96 1.93 1.51
3.12 1.10 1.09 1.07 1.07 1.05 1.13 1.05 1.06 1.06 1.10 1.02 2.17
4.0 3.5 3.0 2.5 2.0 1.5
f1 (ppm)
1.00 1.00 1.06 1.05 3.12 1.10 1.09 1.07 1.07 1.05 1.13 1.05 1.06 1.06 1.10 1.02 2.17 5.41 3.15 3.28
2.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

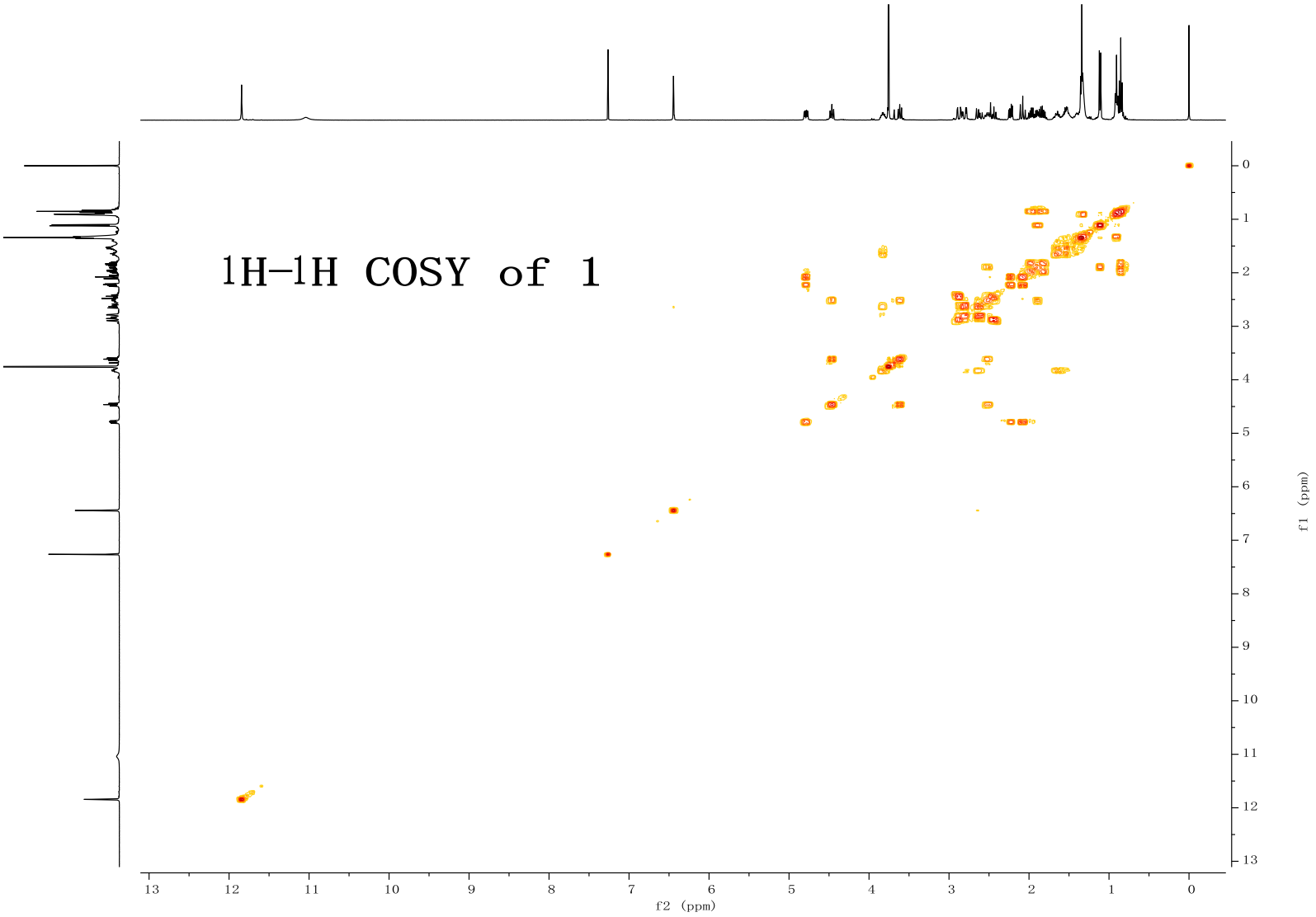

171.41
162.03
151.64
141.33
112.47
109.86
108.55
99.81
77.06
73.52
67.88
52.15
49.50
45.94
36.27
34.43
33.64
31.73
25.05
22.56
14.02
11.61
7.53
O
OH
O
O
OH
H3C
H
O
CH3
3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

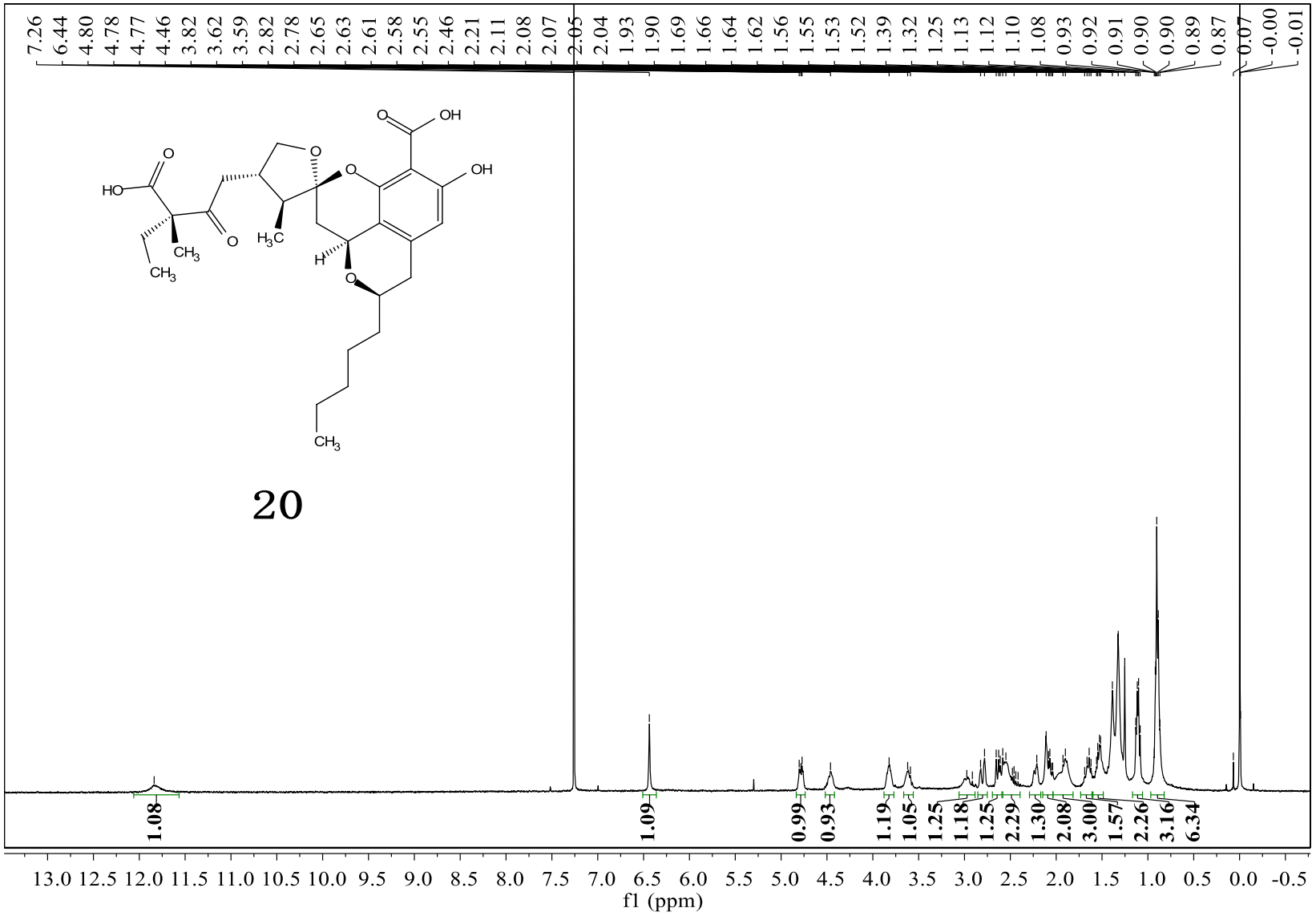

19
f1 (ppm)

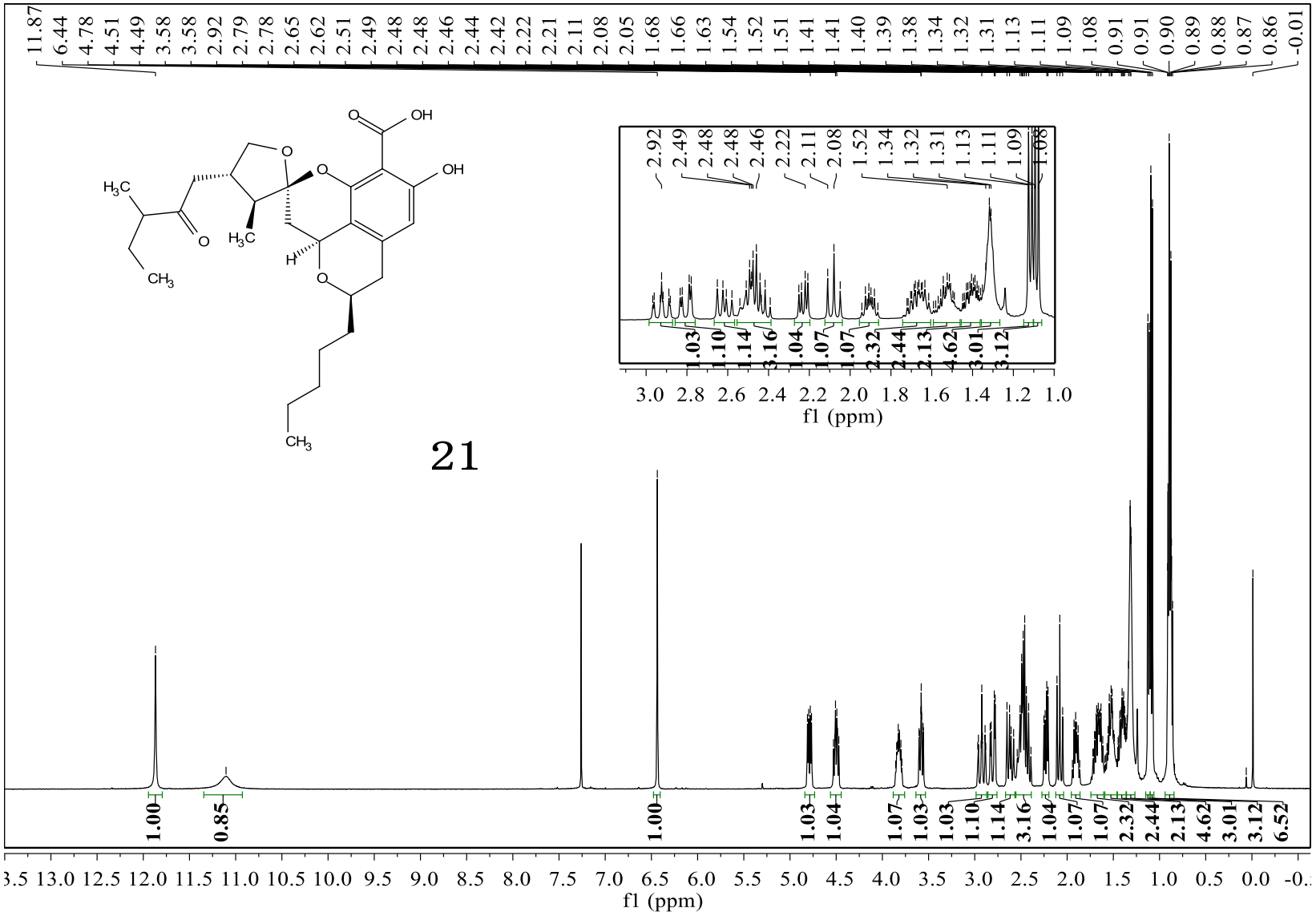

206.75
173.38
171.54
162.04
151.86
141.17
112.46
108.57
108.36
99.93
75.06
72.81
68.07
59.80
52.37
52.13
48.22
41.61
38.86
36.28
34.44
33.60
31.73
27.82
25.04
22.56
18.35
14.00
11.55
8.62
19
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

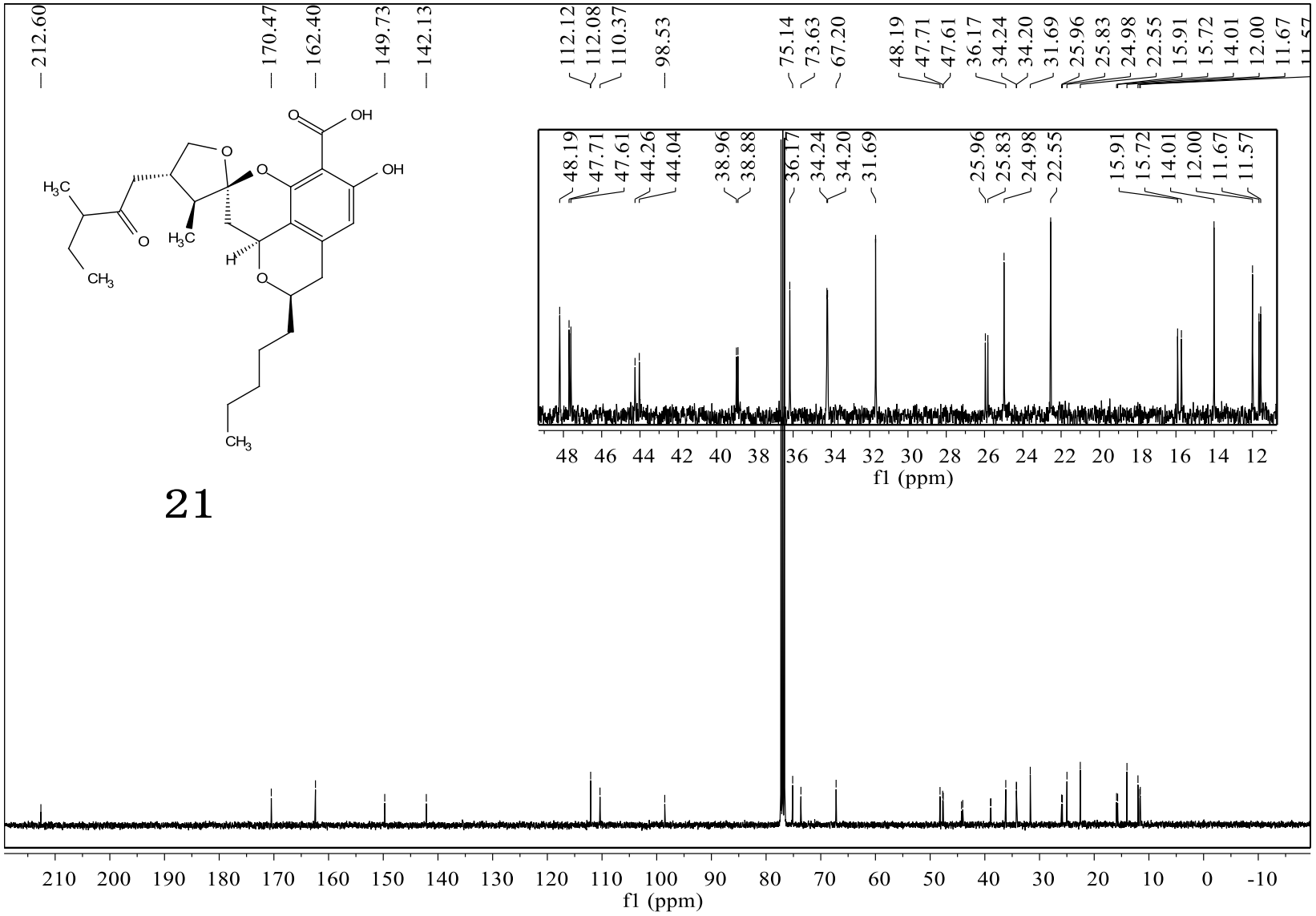

11.82 6.42 4.76 4.44 4.42 3.73 3.61 3.59 3.59 3.57 2.88 2.87 2.83 2.83 2.77 2.76 2.63 2.61 2.46 2.42 2.23 2.22 2.20 2.19 2.09 2.06 2.02 1.95 1.93 1.89 1.88 1.85 1.83 1.81 1.79 1.53 1.51 1.50 1.33 1.32 1.31 1.30 1.10 1.08 0.90 0.88 0.87 0.85 0.83 0.81
OH
OH
O
O
O
O
O
O
H3C
CH3
CH3
H3C
H
O
CH3
1
2.87 2.83 2.77 2.46 2.42 2.20 2.19 2.09 2.06 1.83 1.81 1.51 1.50
2000
1000
0
1.01 1.17 1.30 1.06 1.10 1.12 1.12 1.15 0.95 1.43 1.30 3.06
3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6
f1 (ppm)
1.02 1.03 1.04 1.08 1.06 1.15 3.17 1.06 1.01 1.17 1.30 1.06 1.10 1.12 1.12 1.15 0.95 1.43 1.30 3.06 1.43 3.15 3.00 2.93 3.30 3.18
13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.
f1 (ppm)

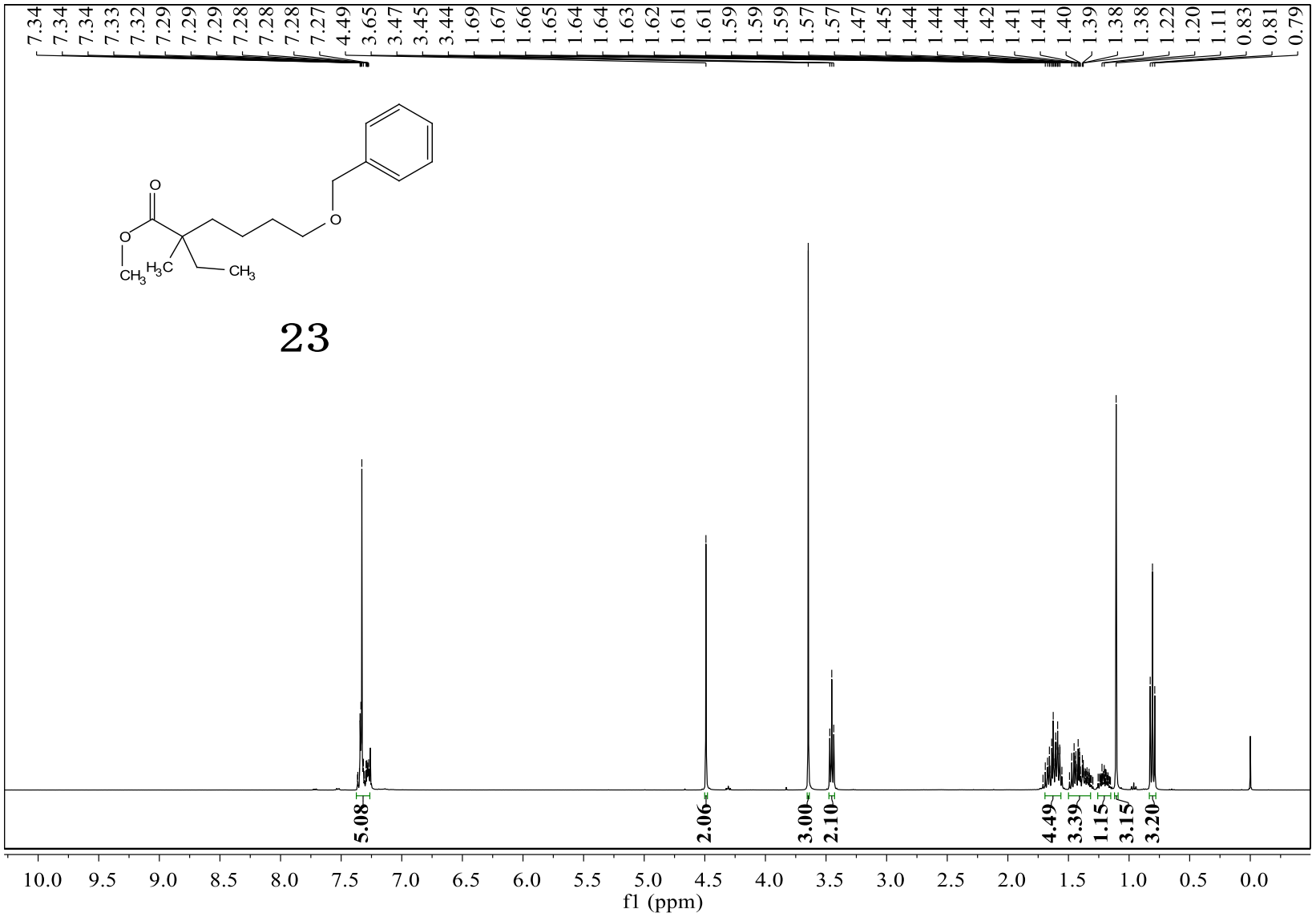

206.00
173.35
170.47
162.56
149.78
142.21
112.20
110.51
98.66
75.22
73.53
67.26
59.78
52.47
48.24
41.58
39.40
36.27
34.34
34.33
31.77
27.95
25.03
22.59
18.43
18.36
14.03
12.00
8.68
OH
OH
O
O
O
O
O
O
O
H3C
CH3
CH3
H3C
H
CH3
1
34.34
34.33
34.6 34.5 34.4 34.3 34.2 34.1
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

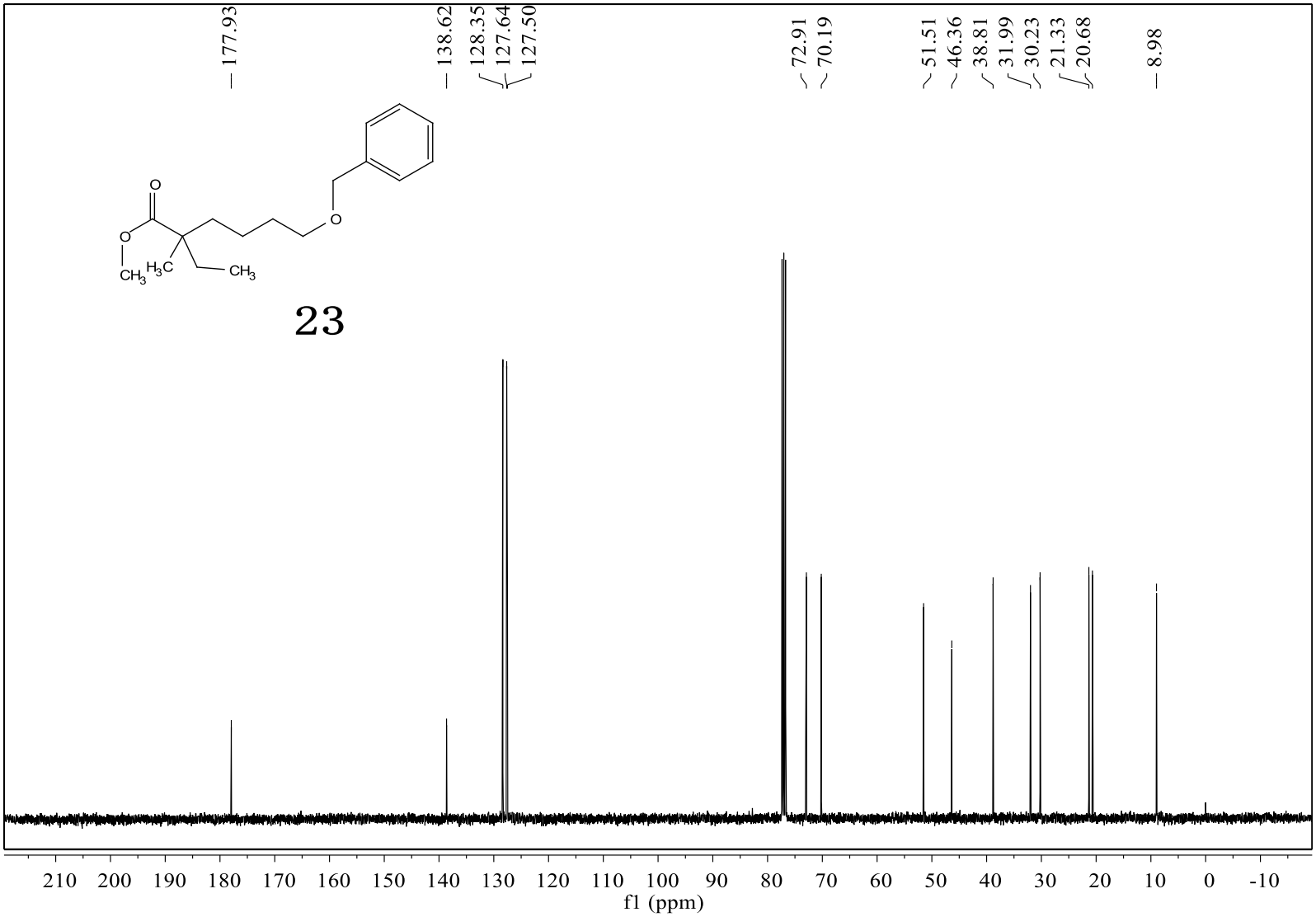

1H–1H COSY of 1
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f2 (ppm)
0
1
2
3
4
5
6
7
8
9
10
11
12
13
f1 (ppm)

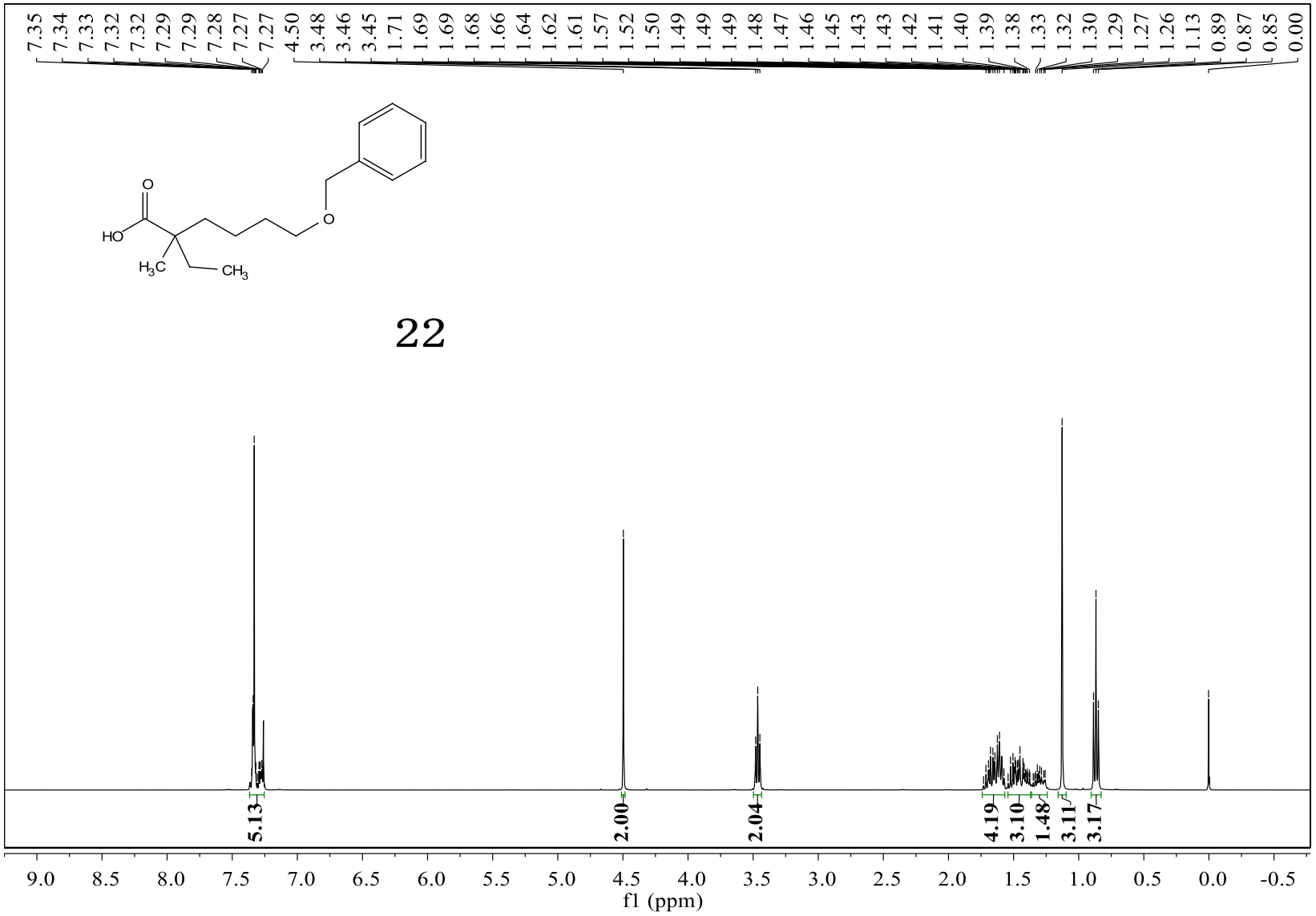

7.26 6.44 4.80 4.78 4.77 4.46 3.82 3.62 3.59 2.82 2.78 2.65 2.63 2.61 2.58 2.55 2.46 2.21 2.11 2.08 2.07 2.05 2.04 1.93 1.90 1.69 1.66 1.64 1.62 1.56 1.55 1.53 1.52 1.39 1.32 1.25 1.13 1.12 1.10 1.08 0.93 0.92 0.91 0.90 0.90 0.89 0.87 0.07 -0.00 -0.01
HO
O
O
CH3
CH3
O
H3C
O
O
H
O
OH
OH
CH3
20
1.08 1.09 0.99 0.93 1.19 1.05 1.25 1.18 1.25 2.29 1.30 2.08 3.00 1.57 2.26 3.16 6.34
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

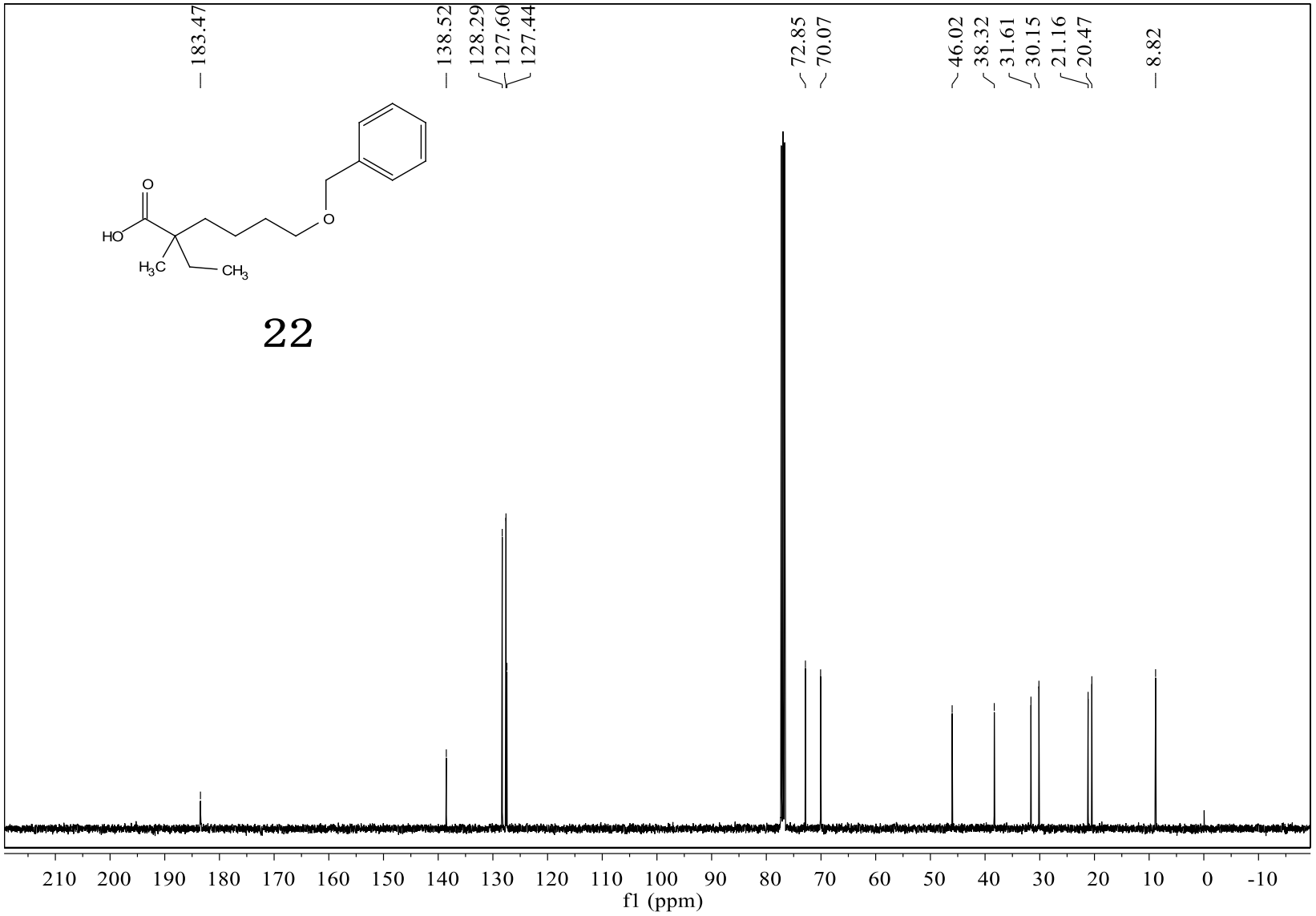

11.87 6.44 4.78 4.51 4.49 3.58 3.58 2.92 2.79 2.78 2.65 2.62 2.51 2.49 2.48 2.48 2.46 2.44 2.42 2.22 2.21 2.11 2.08 2.05 1.68 1.66 1.63 1.54 1.52 1.51 1.41 1.41 1.40 1.39 1.38 1.34 1.32 1.31 1.13 1.11 1.09 1.08 0.91 0.91 0.90 0.89 0.88 0.87 0.86 -0.01
OH
OH
O
O
O
O
H3C
H3C
H
CH3
CH3
21
2.92 2.49 2.48 2.48 2.46 2.22 2.11 2.08 1.52 1.34 1.32 1.31 1.13 1.11 1.09 1.08
1.03 1.10 1.14 3.16 1.04 1.07 1.07 2.32 2.44 2.13 4.62 3.01 3.12
3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0
f1 (ppm)
1.00 0.85 1.00 1.03 1.04 1.07 1.03 1.03 1.10 1.14 3.16 1.04 1.07 1.07 2.32 2.44 2.13 4.62 3.01 3.12 6.52
3.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.
f1 (ppm)

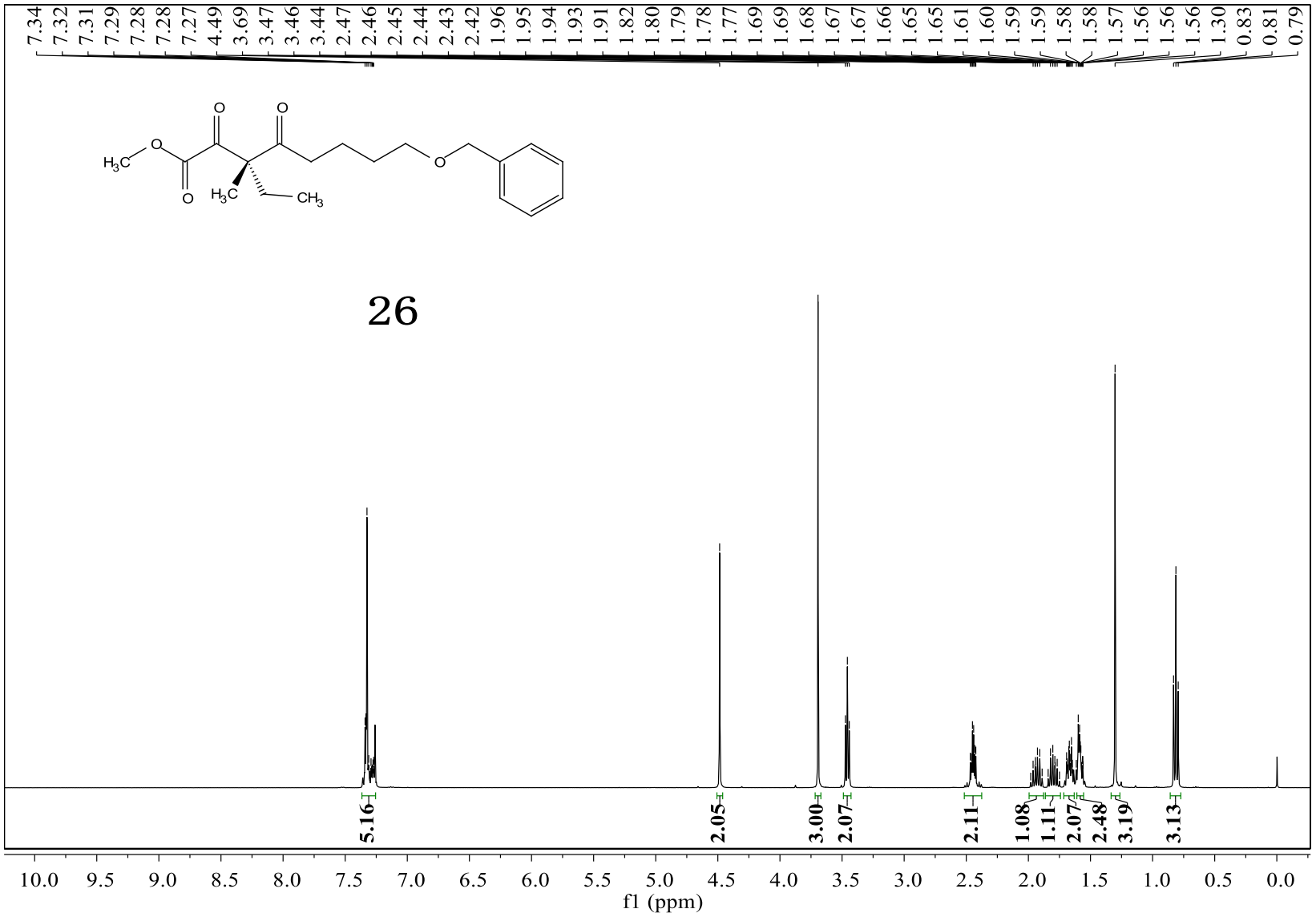

212.60
170.47
162.40
149.73
142.13
112.12
112.08
110.37
98.53
75.14
73.63
67.20
48.19
47.71
47.61
36.17
34.24
34.20
31.69
25.96
25.83
24.98
22.55
15.91
15.72
14.01
12.00
11.67
11.57
OH
OH
O
O
O
O
H3C
H3C
CH3
CH3
H
21
f1 (ppm)
f1 (ppm)

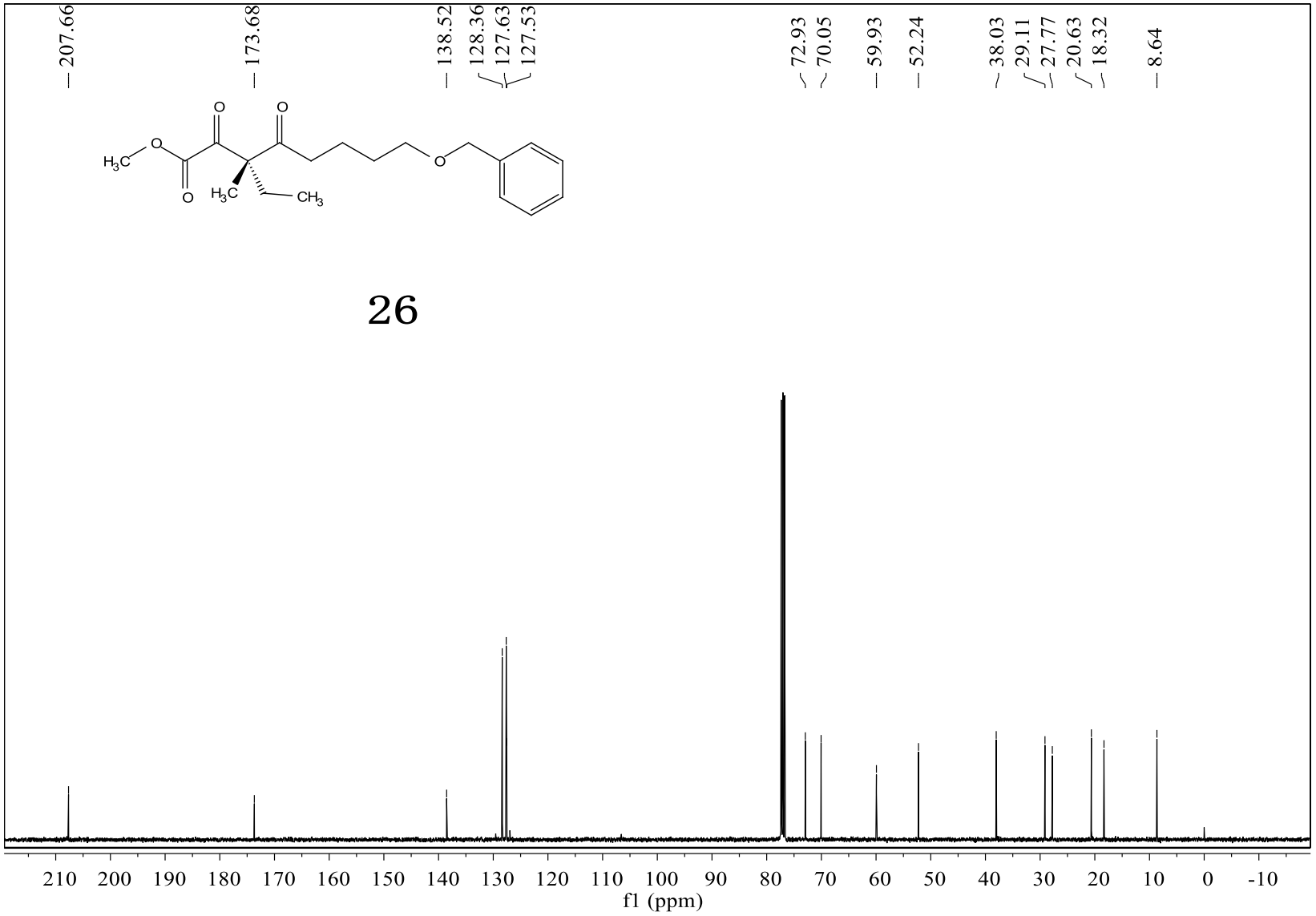

7.34 7.34 7.34 7.33 7.32 7.29 7.29 7.29 7.28 7.28 7.28 7.27 4.49 3.65 3.47 3.45 3.44 1.69 1.67 1.66 1.65 1.64 1.64 1.63 1.62 1.61 1.61 1.59 1.59 1.59 1.57 1.57 1.47 1.45 1.44 1.44 1.44 1.42 1.41 1.41 1.40 1.39 1.38 1.38 1.22 1.20 1.11 0.83 0.81 0.79
O
O
O
CH3
H3C
CH3
23
5.08
2.06
3.00
2.10
4.49
3.39
1.15
3.15
3.20
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

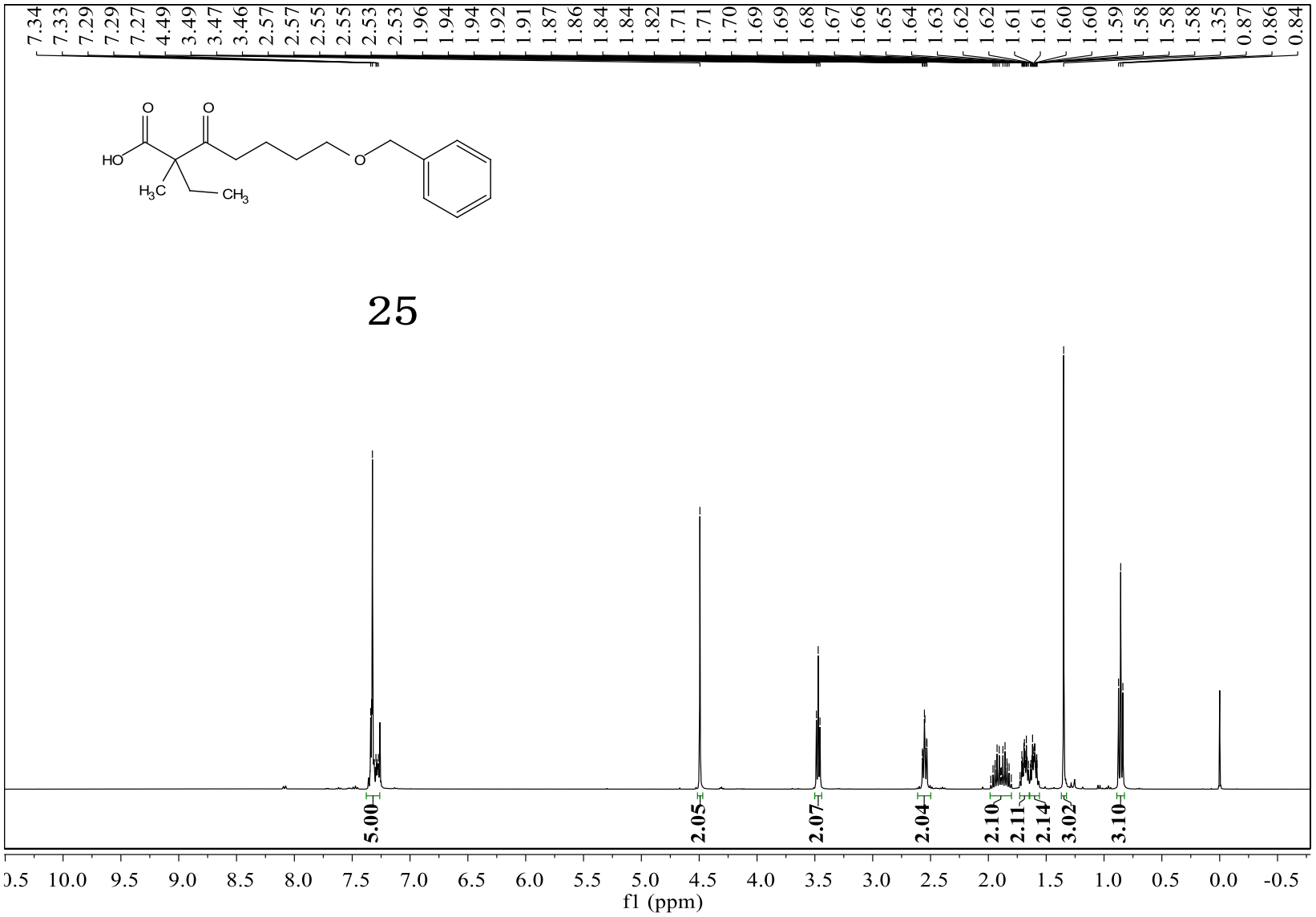

177.93
138.62
128.35
127.64
127.50
72.91
70.19
51.51
46.36
38.81
31.99
30.23
21.33
20.68
8.98
O
O
O
CH3
H3C
CH3
23
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

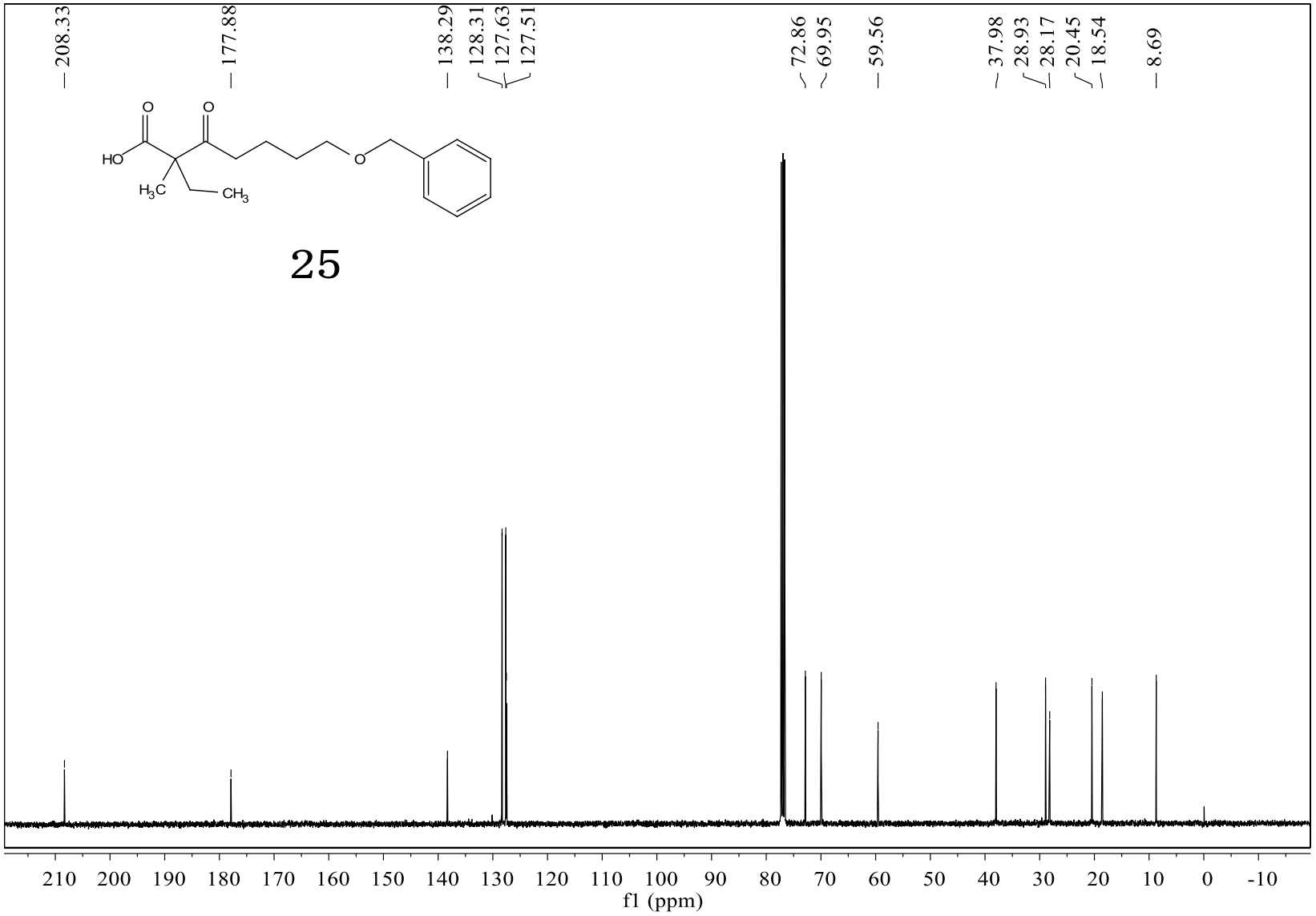

7.35 7.34 7.33 7.32 7.32 7.29 7.29 7.28 7.27 7.27
4.50 3.48 3.46 3.45 1.71 1.69 1.69 1.68 1.66 1.64 1.62 1.61 1.57 1.52 1.50 1.49 1.49 1.49 1.48 1.47 1.46 1.45 1.43 1.43 1.42 1.41 1.40 1.39 1.38 1.33 1.32 1.30 1.29 1.27 1.26 1.13 0.89 0.87 0.85 0.00
O
HO
O
H3C
CH3
22
5.13
2.00
2.04
4.19
3.10
1.48
3.11
3.17
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

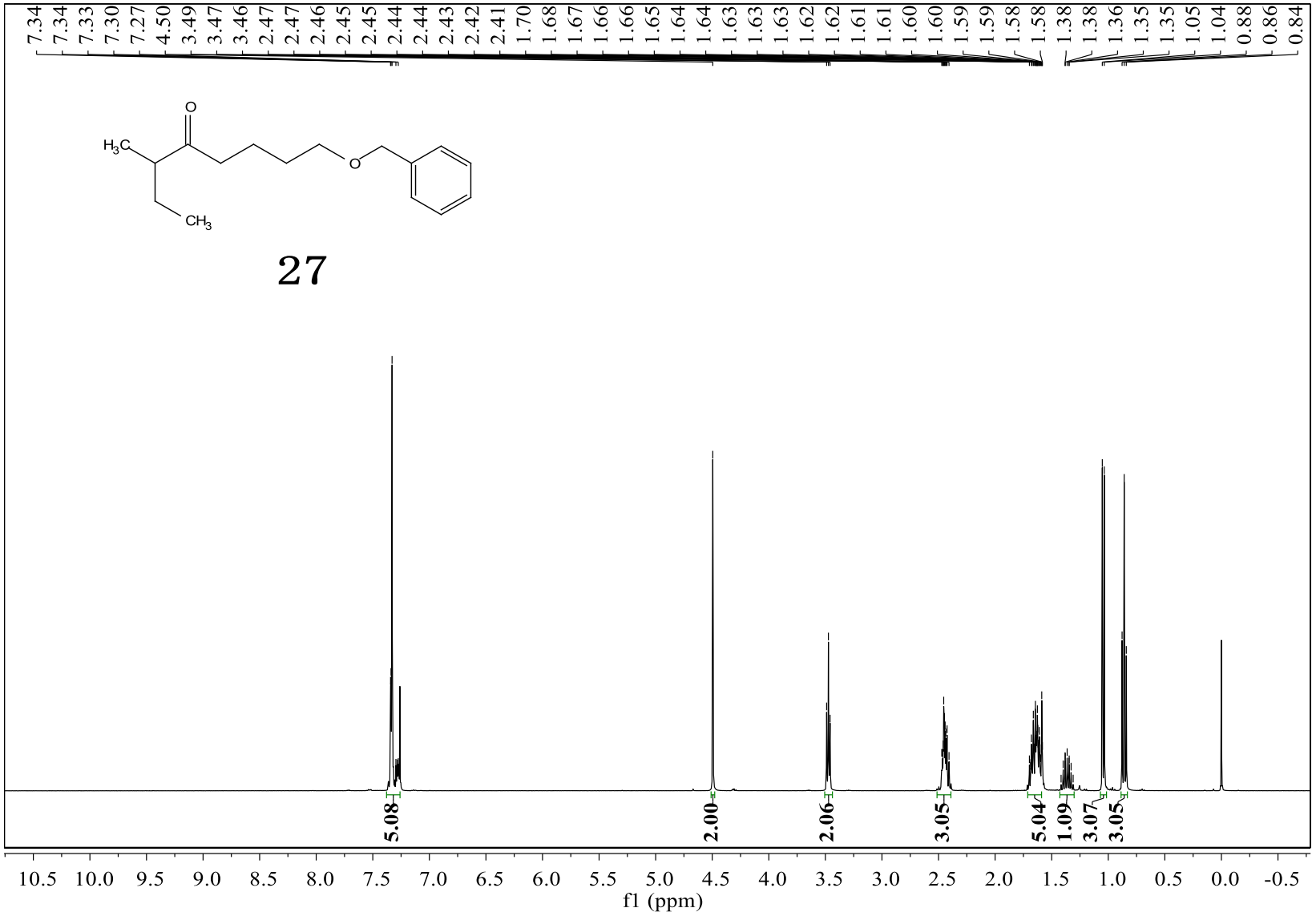

183.47
138.52
128.29
127.60
127.44
72.85
70.07
46.02
38.32
31.61
30.15
21.16
20.47
8.82
O
HO
O
H3C
CH3
22
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

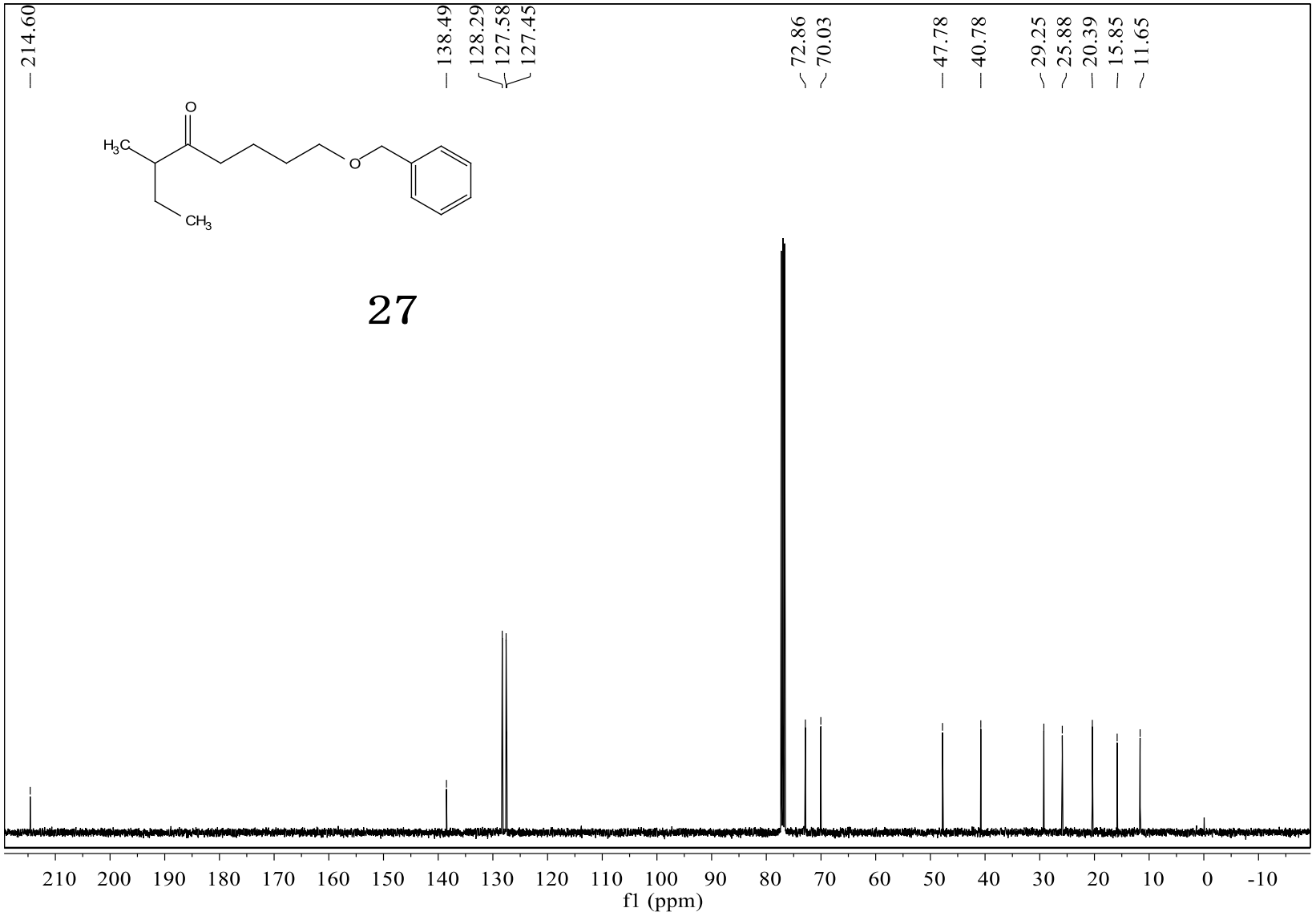

7.34 7.32 7.31 7.29 7.28 7.28 7.27 4.49 3.69 3.47 3.46 3.44 2.47 2.46 2.45 2.44 2.43 2.42 1.96 1.95 1.94 1.93 1.91 1.82 1.80 1.79 1.78 1.77 1.69 1.69 1.68 1.67 1.67 1.66 1.65 1.65 1.61 1.60 1.59 1.59 1.58 1.58 1.57 1.56 1.56 1.56 1.30 0.83 0.81 0.79
O
O
O
O
H3C
O
H3C
CH3
26
5.16
2.05
3.00
2.07
2.11
1.08
1.11
2.07
2.48
3.19
3.13
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


207.66
173.68
138.52
128.36
127.63
127.53
72.93
70.05
59.93
52.24
38.03
29.11
27.77
20.63
18.32
8.64
O
O
O
O
O
H3C
H3C
CH3
26
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.34 7.33 7.29 7.29 7.27 4.49 3.49 3.47 3.46 2.57 2.57 2.55 2.55 2.53 2.53 1.96 1.94 1.94 1.92 1.91 1.87 1.86 1.84 1.84 1.82 1.71 1.71 1.70 1.69 1.69 1.68 1.67 1.66 1.65 1.64 1.63 1.62 1.62 1.61 1.61 1.60 1.60 1.59 1.58 1.58 1.58 1.35 0.87 0.86 0.84
HO
O
O
O
H3C
CH3
25
5.00
2.05
2.07
2.04
2.10
2.11
2.14
3.02
3.10
f1 (ppm)


208.33
177.88
138.29
128.31
127.63
127.51
72.86
69.95
59.56
37.98
28.93
28.17
20.45
18.54
8.69
O
O
HO
O
H3C
CH3
25
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.34 7.34 7.33 7.30 7.27 4.50 3.49 3.47 3.46 2.47 2.47 2.46 2.45 2.45 2.44 2.44 2.43 2.42 2.41 1.70 1.68 1.67 1.66 1.66 1.65 1.64 1.64 1.63 1.63 1.63 1.62 1.62 1.61 1.61 1.60 1.60 1.59 1.59 1.58 1.58 1.38 1.38 1.36 1.35 1.35 1.05 1.04 0.88 0.86 0.84
O
H3C
O
CH3
27
5.08
2.00
2.06
3.05
5.04
1.09
3.07
3.05
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


214.60
138.49
128.29
127.58
127.45
72.86
70.03
47.78
40.78
29.25
25.88
20.39
15.85
11.65
O
H3C
O
CH3
27
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)